Evidence-based and clinical views on acute wound healing and scar formation
Brölmann, Fleur

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Evidence-based and clinical views on acute wound healing and scar formation

Fleur Eline Bröllmann
Evidence-based and clinical views on acute wound healing and scar formation
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Evidence-based and clinical views on acute wound healing and scar formation
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Faculteit der Geneeskunde
Aan mijn lieve papa
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General introduction and outline of this thesis
General introduction and outline of this thesis

Clinical scenario

A 43-year-old woman, bitten on her calf by a dog, consults her general practitioner (GP). The GP provides the standard local wound care according to the national recommendations for GPs, leaving the wound open after disinfection. The GP decides not to prescribe prophylactic antibiotics as the wound is located on the leg. After a week, the woman returns to her GP with a fever. The affected leg is painful, swollen and red, and the wound size has increased over time. The GP refers the patient to hospital, fearing the need for extensive debridement.

In the local hospital the wound is cleansed with saline solution in the emergency department. During the patient’s hospital stay, a culture swab is taken of the wound before the patient is administered systemic antibiotics and a general surgeon performs sharp wound debridement. After several days, the infection has been successfully eliminated and a superficial granulating wound remains. The surgeon, however, considers the chances of a recurrence of infection to be too high to let the wound heal by secondary intention. The surgeon explains to the patient that he would prefer to encourage primary wound closure by means of a skin transplant. Although the patient wonders whether the donor site wound on her thigh will leave an unsightly scar when wearing her bathing suit, she is reluctant to ask this question, believing that this is apparently the sacrifice she will have to make in order for her initial wound to heal.

Immediately after the skin-harvesting procedure, the operation assistant asks the surgeon which wound dressing to apply to the donor-site wound. Because convincing evidence is lacking, the surgeon suggests a hydrofibre dressing, as this is the standard local practice. The patient returns to the surgical ward with this dressing applied to the donor site. After a few days her nurse consults the wound specialist because of a dark yellow slough on the hydrofibre dressing. The wound specialist informs the patient and the nurse about the (normal) characteristics of the dressing material and the associated wound-healing process. After five days the graft has almost completely taken and the patient is discharged.

After being at home for some time, the patient consults her GP regarding the expected wound healing of the donor site and fading of the scar over time. On reviewing the discharge papers, the GP merely finds information on the
acceptor-site wound and the split skin graft operation, but nothing about the expected outcome for the donor site.

This everyday clinical scenario exposes several issues arising from the care of such acute wounds: 1) patients with acute wounds deal with medical staff from various disciplines; 2) wound care is often based on clinical experience or preference; and 3) evidence-based guidelines or local protocols are lacking, or the available evidence is not habitually implemented in daily clinical practice. Last, but not least, patient preferences should be actively and repeatedly sought and integrated in wound care.

Thus, this scenario also demonstrates typical wound-related issues that are not in agreement with evidence-based practice, which ideally integrates patient preferences, clinical expertise and the best available evidence in clinical decision making.\(^1\)

**Aim of the thesis**

The overall aim of this thesis is to give an insight into the practice of evidence-based wound care. We therefore investigated:

1. Evidence generation in (acute) wound care (part I);
2. The assessment of scar formation and the patients’ appreciation of their scar formation (part II);
3. The integration of available evidence on acute wound care and clinical views and expertise in the form of a clinical interdisciplinary evidence-based guideline (part III).

**Acute wound healing (part I)**

Wound healing is the physiological response of the body to injury, regardless of its aetiology. The normal healing process follows four phases, namely haemostasis, inflammation, proliferation (epithelialisation) and remodelling.\(^2,3\) These phases occur in a relatively predictable fashion and should preferably result in the sustained restoration of anatomic and functional integrity.\(^4-6\) In this thesis, acute wounds are defined as wounds with an acute aetiology that undergo the healing process in a timely and orderly manner.

As was described in the clinical scenario, however, acute wounds have the potential to become complex wounds (e.g. due to wound infection). In such cases, the physiological healing cascade is disturbed and it fails to repair the tissue injury. This is defined as complex or chronic wound healing.\(^2,7,8\) This boundary between acute and complex
wounds (formerly known as chronic wounds) overlaps in the current literature and in clinical practice, and can therefore cause confusion.\textsuperscript{9} The introduction of the term complex wound healing instead of chronic wound healing is a result of this intangible definition in wound care practice.\textsuperscript{10}

Complex wounds are a major cause of morbidity in patients and are a cost burden to hospitals and community healthcare providers, and their decision makers.\textsuperscript{2,8,11,12} Up-to-date international incidence or prevalence estimates of acute wounds are lacking.\textsuperscript{3,13,14} In the Netherlands alone, about 420,000 patients were treated in emergency rooms in the year 2012 for acute wounds resulting from accidents or self-mutilation (e.g. superficial skin injury (63%), open wounds (35%), traumatic amputation (<1%), burns, or frostbites (3%)).\textsuperscript{15}

In this thesis “wound care” is comprised of the treatment (generally provided by doctors) as well as the care for wounds (often provided by nurses or caregivers), as these two components are strongly interconnected. In order for health professionals to provide optimal wound care in daily practice, the availability of convincing evidence on wound care is highly desirable. However, niches in evidence-based wound care may occur, both in terms of the quantity of publications as well as in the level of evidence these publications offer. To appreciate the quality and quantity of the available evidence in wound care, we will compare worldwide publication trends in two distinct areas of medical expertise (Chapter 2). After identifying high-quality evidence on local and systemic wound care, we will provide clinicians with an overview of the conclusions and supply recommendations for applying this evidence in clinical decision making (Chapter 3). To improve the generation of high-quality evidence in wound care, recommendations as to the design, conducting and reporting of randomised clinical trials (RCTs) will be described in Chapter 4 and Chapter 5. As convincing evidence about which dressing material is most effective for covering acute donor-site wounds is lacking, we will try to answer this research question using a multicentre RCT called “the Rembrandt trial” (Chapter 6).

**Scar formation (part II)**

Scar formation is the last phase of normal wound healing, as was explained above. This remodelling phase can take 12 months to several years.\textsuperscript{16-18} The clinical manifestation of the remodelling phase includes contraction, decreased redness, decreased thickness, decreased induration, and increased strength.\textsuperscript{19} Scars occur after almost every skin injury, except for superficial wounds (e.g. tattoos and scratches) or in early mammalian
Each year in the developed world, 100 million patients acquire scars as a result of 55 million elective operations and 25 million operations required after trauma. Some of these scars, however, cause considerable problems. Just as the patient in the clinical scenario wonders about the final outcome of her scar, in the perception of patients, scars can be disfiguring, aesthetically unpleasant, and may cause itching, tenderness and pain. When located in visible areas, scars have a psychological impact and could affect quality of life. Furthermore, scars can develop into dysfunctional scar contractures with severe deformities and cause a significant reduction in a patient's daily activities. The current evidence for scar treatment strategies is poor.

As a prerequisite for treating scars, accurate scar assessment is essential for the diagnosis and the initiation, monitoring and evaluation of scar treatment. The Observer Scar Assessment Scale (OSAS) is used to judge scars in vivo and on digital photographs. It is questionable whether these different methods influence the results of the scar assessment. In Chapter 7 we will assess the inter-method reliability and score agreement, and perform validity testing of in vivo and digital photographic assessments of donor-site scars.

Furthermore, we will conduct an inter-observer and patient analysis in order to investigate the agreement between caregivers and patients on the scar quality of donor-site wounds using the Patient and Observer Scar Assessment Scale (POSAS) (Chapter 8). As scar maturation evolves over time, the scar quality of patients with donor-site wounds will be compared after three and after at least six months in order to detect any relevant patient-perceived issues (Chapter 9). These issues could benefit from timely action to try and prevent further progression early in the remodelling phase.

**Guideline development (part III)**

Evidence on the use of prophylactic antibiotics for mammalian wounds, the treatment of donor-site wounds, and scar assessment exists and should be used in clinical decision making, as outlined in the clinical scenario above. Regardless of the quality of this available evidence, clinicians should be offered accessible and useful documents to guide them in making wound-care decisions.

Evidence-based guidelines aim to present recommendations based on the relevant evidence and clinical expertise, combined with patient preferences. In general, but also in wound care, guidelines help physicians make evidence-based decisions, taking into account not only the impact on outcome, but also the risk–benefit ratio of particular
wound materials or strategies. However, apart from the National Institute for Health and Care Excellence (NICE) guidance on the prevention and treatment of surgical-site infections (SSI), national and international evidence-based guidelines for acute wounds are lacking. The development of such a guideline is desirable because it will:

- Enhance uniformity between medical disciplines and settings;
- Improve the quality and effectiveness of wound care; and
- Help bridge the gap between desirable evidence-based use and actual use of this scientific knowledge in clinical wound practice.  

In order to develop a valid and evidence-based guideline, use of the Appraisal of Guidelines and Research and Evaluation (AGREE II) criteria is recommended. We will therefore develop an evidence-based guideline, according to the AGREE II criteria, for wounds with an acute aetiology (Chapter 10). This guideline will focus on a selection of the most pressing wound-care issues as perceived by the experts in the working group.

Finally, this thesis will conclude with a discussion of the future perspectives, implementation strategies and a summary of the findings in (acute) wound care.
References


part I

Acute wound healing
Does evidence permeate all surgical areas equally? Publication trends in wound care compared to breast cancer care: a longitudinal trend analysis

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D.T. Ubbink
H. Vermeulen

World Journal of Surgery 2012
Abstract

Background
Evidence-based decision making has permeated the daily practice of healthcare professionals. However, in wound care this seems more difficult than in other medical areas, such as breast cancer, which has a similar incidence, variety of etiologies, financial burden, and diversity of treatment options. This incongruence could be due to a lack in quantity and quality of available evidence. We therefore compared worldwide publication trends to answer whether research in wound care lags behind that in breast cancer.

Methods
In order to assess the trends in quantity and methodological quality of publications as to wound care and breast cancer treatments, we examined relevant publications over the last five decades. Publications in MEDLINE were classified into seven study design categories: (1) guidelines, (2) systematic reviews (SR), (3) randomized (RCT), and controlled clinical trials (CCT), (4) cohort studies, (5) case-control studies, (6) case series and case reports, and (7) other publications.

Results
We found a 30-fold rise in publications on wound care, versus a 70-fold increase in those on breast cancer. High-quality study designs like SR, RCT, or CCT were less frequent in wound care (difference 1.9, 95 % CI 1.8–2.0 %) as were guidelines; 76 on wound care versus 231 for breast cancer.

Conclusions
Publications on wound care fall behind in quantity and quality as compared to breast cancer. Nevertheless, SR, RCT, and CCT in wound care are becoming more numerous. These high-quality study designs could motivate clinicians to make evidence-based decisions and researchers to perform proper research in wound care.
Introduction

Every day, surgeons are charged with solving decisional dilemmas while taking care of their patients. Ideally, such choices are based on best available evidence, clinical expertise, and patient preferences. This evidence-based decision making has gradually permeated the daily practice of modern healthcare professionals\(^1\)-\(^3\) and is endorsed by the U.S. National Institute of Medicine.\(^4\) It is safe to say that nowadays no surgical area is exempt from the obligation to generate and use convincing evidence in the practice of high-quality patient care. However, the principle of evidence-based practice has not been implemented equally among all surgical areas.\(^5\) For example, in wound care, evidence-based decision making seems to flourish less than in many other medical areas.\(^6\) The reason for this is unclear, particularly considering the financial impact, prevalence, and effect on quality of life that make wound care a serious health care burden that needs to be relieved by proper evidence.\(^7\)-\(^11\)

A representative illustration of the situation in another surgical area is found in breast cancer. This is a disorder in which huge amounts of money have been invested for research purposes. Although this disorder is obviously different from wounds, it has remarkable similarities in terms of being a surgical disorder characterized by a large diversity of etiologies, treatment options, and outcomes measured.\(^12\) In addition, the lifetime risks of acquiring breast cancer or a (chronic) wound are similar; roughly one of out every ten subjects.\(^7,13\)-\(^18\) Hence, one might think these two disorders deserve equal research efforts and similarly sized bodies of knowledge to enable evidence-based decision making.

Any discrepancy in evidence-based decision making between the areas of breast cancer and wound care could be due to a difference in the amount of convincing evidence available. Such evidence is preferably derived from systematic reviews (SR), randomized (RCT), or controlled clinical trials (CCT).\(^2\) However, particularly in the realm of wound care, opinion-based articles conclude that the mainstay of evidence seems to consist of noncomparative research designs, which are much more sensitive to bias.\(^6,12,19,20\) This is articulated by frequent appeals in the conclusion of Cochrane systematic reviews: “evidence is weak, so further research is required to validate these findings.”\(^21\)-\(^25\)

We hypothesize that a lack of convincing evidence in wound care forms a barrier for surgeons to practice evidence-based healthcare. Because the quantity and quality of evidence play a crucial role in decision making, it is interesting to know whether and why empirical evidence features more largely in some medical areas than in others. For this reason, we analyzed and compared the worldwide trends as to the quantity and
quality of publications regarding wound care and breast cancer, to answer the following question: Is wound care research behind the times in terms of good quality publication output as compared to breast cancer? The answer to our research question could provide surgeons with information about whether high-quality evidence is available for wounds to promote evidence-based practice in wound care to the same degree that applies in breast cancer. This will also help surgeons with clinical and economical decision making to ensure optimum quality of care.

Methods

We identified all relevant scientific publications over the last 5 decades concerning wound and breast cancer treatments. We did not exclude publication types like letters, editorials, or comments because publication types incorrectly tagged could be missed using search filters. Search strategies were designed in cooperation with a medical information specialist. We searched MEDLINE from 1961 to 2010 by means of two interfaces: OVID for a wide-ranging search of all publication types, followed by PubMed to find particular guidelines. The general search strategies from the Cochrane Wounds Group and the Cochrane Breast Cancer Group were used (see Electronic Supplementary Material). To distinguish the various study designs, these searches were combined with filters available from the BMJ (British Medical Journal) Evidence Centre, the Cochrane Collaboration and Scottish Intercollegiate Guidelines Network (SIGN) (see Electronic Supplementary Material). We did not apply any search limitations such as publication year, type of article, or language.

Subsequently, the selected publications were classified into one of seven study design categories: (1) guidelines, (2) SR, (3) RCT and CCT, (4) cohort studies, (5) case-control studies, (6) case series and case reports, and (7) other publications. Realizing that the available filters for specific study designs are not perfect, we validated our search strategy by means of spot-checks of the publications found in both disorders. For this purpose, we randomly chose 100 publications from each study design and in three different 5-year periods to validate the search filter. Titles and abstracts were screened independently by two researchers as to which study design was used and whether this matched the filters used. All search strategies were adapted until the highest number of correct study designs was found with the lowest number of erroneous ones. Adaptations were made by excluding MESH terms like “*peptic ulcer/* “*colitis, ulcerative/* “*eye infections”, or by adding terms like “wound$.ti” and “traumatic wound$.ti”.

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Finally, PubMed was independently searched by two researchers to find guidelines. These were checked for relevance; i.e., they should address screening, prevention, etiology, pathology, diagnosis, or treatment.

**Data analysis**

We calculated how many of the publications found belonged to our predefined publication type categories. The absolute and relative—i.e., in relation to the total in its category—numbers of publications per five years were recorded and plotted as frequency histograms against their publication date. Differences in percentages were calculated including their 95% confidence intervals (CI).

**Results**

**Quantity and quality of publications**

Over the last 5 decades we found a total of 145,114 publications on wound care and 217,484 on breast cancer treatment. For wound and breast cancer treatment alike, the majority of publications were classified as “other publications” (65.6 vs. 72.5 %, respectively), as detailed in the paragraph below.

Differences in quality are illustrated in Fig. 1, which gives an overview of the different study designs (categories 2–6). Studies on wound care were significantly more...
observational than those on breast cancer (31.2 vs. 22.2 %, respectively; difference 9.0, 95 % CI 8.7–9.3). In addition, the proportion of case series and case reports was significantly higher in wound care (20.5 %) than in breast cancer publications (10.2 %; difference 10.3, 95 % CI 10.0–10.5). Only a very small percentage of the articles (wound care 3.1 %; breast cancer 5.3 %) could be classified as SR, RCT, or CCT, but significantly more on breast cancer (difference 2.16, 95 % CI 2.03–2.29). Thus, over twice as many RCT and CCT were available on breast cancer treatment (10,186) as on wound care (4,061).

**Verification of study categorization: other publications**

By means of spot-checks, 100 randomly selected publications in three five-year periods, 1981–1985, 1991–1995, and 2001–2005, were re-categorized by hand, to verify the study type as indicated by the search filter and to check the types of publications grouped in the relatively large category of “other publications.” Over 90 % of the category 2 through 6 study types was found to be correctly classified by the search filters. About three quarters of the spot-check publications were confirmed as “other publications” (Table 1). The remainder, 21.7 % in wounds and 25.7 % in breast cancer, were re-categorized as clinical trial or observational study.

<table>
<thead>
<tr>
<th>Other publications</th>
<th>Wound Care Records (%)</th>
<th>Breast Cancer Records (%)</th>
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<tbody>
<tr>
<td>Publications incorrectly categorized as “other publications”</td>
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<tr>
<td>Clinical trial</td>
<td>5 (1.6)</td>
<td>3 (1.0)</td>
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<tr>
<td>Observational studies</td>
<td>62 (20.7)</td>
<td>74 (24.7)</td>
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<tr>
<td>Subtotal</td>
<td>65 (21.7)</td>
<td>77 (25.7)</td>
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<tr>
<td>Publications correctly categorized as “other publications”</td>
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<td></td>
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<tr>
<td>(Narrative) review</td>
<td>55 (18.3%)</td>
<td>70 (23.3%)</td>
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<tr>
<td>Pilot evaluation</td>
<td>-</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Laboratory studies (in vitro)</td>
<td>60 (20.0%)</td>
<td>46 (15.3%)</td>
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<tr>
<td>Animal studies or plant studies</td>
<td>19 (6.3%)</td>
<td>5 (1.6%)</td>
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<tr>
<td>Letter, comment or editorial</td>
<td>17 (5.7%)</td>
<td>17 (5.7%)</td>
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<tr>
<td>Unknown (e.g. insufficient information available)</td>
<td>80 (26.7%)</td>
<td>83 (27.7%)</td>
</tr>
<tr>
<td>Economic evaluation</td>
<td>4 (1.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Subtotal</td>
<td>235 (78.3)</td>
<td>223 (74.3)</td>
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<td><strong>Total</strong></td>
<td>300 (100)</td>
<td>300 (100)</td>
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**Publication trends in time**

Figures 2 and 3 show the number of publications between 1961 and October 2010 in 5-year intervals for wound care and breast cancer. During the past 50 years, breast cancer publications showed a higher number and a quicker growth than wound care publications. In both disorders, the numbers of publications increased substantially.
However, for wound care this was an approximately 30-fold increase, whereas for breast cancer it was a 70-fold increase. This trend was more pronounced for the number of trials published, i.e., 800-fold for wound care and 1,700-fold for breast cancer.

Fig. 2 Wound care publication trends by study design RCT: randomised clinical trial; CCT: controlled clinical trial.

Fig. 3 Breast cancer publication trends by study design RCT: randomised clinical trial; CCT: controlled clinical trial.
Guidelines

Of the 211 guidelines found for wound care, only 76 (36 %) guidelines were indeed relevant to wound care. The other guidelines contained a diversity of other medical specialties not related to wounds. In contrast, for breast cancer, 231 (90%) of the guidelines found were relevant to breast cancer. Figure 4 shows that the number of wound care guidelines

![Graph showing trends in guideline publications regarding breast cancer and wound care.]

Fig. 4 Trends in guideline publications regarding breast cancer and wound care.

<table>
<thead>
<tr>
<th>Table 2 Guideline subjects for wound care</th>
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<tr>
<td>Acute wounds</td>
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<td>Burns</td>
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<td>SSI</td>
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<td>Chronic wounds</td>
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<td>Other</td>
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<td>Total</td>
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SSI, surgical site infection

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<th>Table 3 Guideline subjects for breast cancer</th>
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<tr>
<td>Screening/diagnostic</td>
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<tr>
<td>Mammography</td>
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<td>Pathology</td>
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<td>Therapy</td>
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<td>Other</td>
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<td>Total</td>
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increased 5.4 times over the last 5 decades, while breast cancer guidelines showed a 15.4-fold increase over the same period of time. Table 2 shows that guidelines for wound care applied mostly to chronic wounds (68%), rather than acute wounds (2%), prevention, diagnosis, or pathology. Table 3 shows a wide variety in terms of screening, diagnostic, and treatment guidelines (73%), whereas mammography (4%) and pathology (4%) guidelines were less published for breast cancer.

Discussion

The results of our study confirm a rising number of publications for both wound care and breast cancer, which is no different from other areas in medicine. However, the quantity of publications on breast cancer is larger and has a more exponential character in time as compared to wound care. Also, the quality of studies in terms of robust study designs differs in favour of breast cancer. Significantly more clinical trials and fewer case series or case reports have been reported on breast cancer than on wound care.

We are convinced that these findings present a message that is valuable for surgeons. Although there is an inequality in robust knowledge on wound care compared to other areas, sound evidence is available and should be taken into account by surgeons in their decision making. Wound care and wound healing are of great value to all surgical patients, despite the tendency among some surgeons to consider wounds as a mere tailpiece of

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<td>3</td>
<td>0</td>
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<td>9</td>
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<td>10</td>
<td>19</td>
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<td>14</td>
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<td>78 (34%)</td>
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<td>2</td>
<td>0</td>
<td>5</td>
<td>9 (4%)</td>
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<tr>
<td>2</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>9 (4%)</td>
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<td>91 (39%)</td>
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<td>44 (19%)</td>
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<td>15</td>
<td>62</td>
<td>70</td>
<td>80</td>
<td>231 (100%)</td>
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surgical procedures. This study should be reason to increase awareness among surgeons of available evidence for wounds.

This study is unique in its kind, as it compares trends in quality and quantity of publication output within these two medical areas. Although no classic examples for this kind of bibliometric research are available to mirror our design and outcomes, we assume our results are likely to be valid. This assumption is based on our use of the generally accepted and sensitive search strategies from the Cochrane Wounds Group and the Cochrane Breast Cancer Group, the spot-checks, and the expertise of our medical information specialist. Furthermore, the spot-checks confirmed the reliability of the different filters used to categorize the studies with exception of the remaining group: other study designs.

Some limitations of our analysis need to be mentioned. First, the searches undertaken as part of this study were performed using the MEDLINE database, which is limited to indexed journals. Wound care research is, probably in contrast to breast cancer research, also distributed through non-indexed journals, which could provide an additional number of case series and case report studies that were not captured in this study. Consequently, our search could have underestimated the proportion of case series and case reports, as well as the total number of wound care publications. When comparing the available high-level evidence in terms of systematic reviews, RCT and CCT, such studies are likely to be published on both disorders alike, possibly fostered by positive publication bias. Adding the attractiveness of breast cancer as a research and societal topic, and the proper scientific evaluation that pharmaceutical treatments for breast cancer require before marketing, it is possible that this kind of research receives more funding and attention than does wound care and is therefore easier to publish. This study clearly shows a difference in publication output between the disorders for which funding, publication bias, and demand are all plausible causes of these differences.

Second, we limited our analysis to the last five decades. However, the numbers of publications found before 1960 were negligible and unlikely to influence the results of the observed publication trends. Furthermore, our aim was to study overall publication trends, rather than to give a complete historical overview of publications.

Third, it is important to consider the advantages and limitations of a broad search strategy. Its main advantage is a high sensitivity. As a consequence, however, more hits irrelevant to our medical area appeared in such a search strategy, which may have caused an overestimation of the quantity of publications in both areas. We assumed that the number of irrelevant hits would be equally high in both groups and would therefore not interfere with our conclusions. A further limitation of this search strategy might have
been the different search strategies used for each medical area. On the other hand, two researchers (M.G. and F.B.) performed the search independently, and their results were similar.

Fourth, the idea of comparing breast cancer to wound care can be questioned. This comparison might seem farfetched, as breast cancer is a malignant, potentially life-threatening disease while suffering from a wound is not. However, both are very similar in terms of their widespread occurrence, disease burden, and variation in etiology, treatment options, outcome measures, and patients affected. This should be reason for a similar urgency to generate strong evidence regarding their treatments.

Finally, using the recently developed filters to retrieve guidelines in PubMed, we often found duplicate guidelines regarding the same topic or articles that did not include a guideline at all. Even though the same filter was used, this problem appeared larger in wound care. The wound care guidelines reported in this article could therefore be an underestimation of the problems in wound care research and should be further explored to produce new research questions relevant to patients and clinicians.

Although the field of wound care appears somewhat smaller and publications do fall behind in quantity and quality, our analysis shows that systematic reviews—RCT and CCT—in wound care are being performed and are even on the rise in the last decades. This knowledge helps in building arguments against those who claim it is hard to design, conduct, or apply sound research in wound care. The small number of (evidence-based) guidelines for wound care, especially for acute wounds, revealed a niche that has to be addressed in the near future to help clinicians in evidence-based decision making and to facilitate evidence-based medicine in the wound care area.

Acknowledgments

We thank David Muldrew for his writing assistance, and the central medical library of the AMC for the literature search.
Chapter 2

References


6. Dumville JC, Petherick ES, Cullum N. When will I see you again? The fate of research findings from international wound care conferences. Int Wound J 2008;5:26–33


Evidence-based decision making for local and systemic wound care

F.E. Bröllmann
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K. Munte
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H. Vermeulen

British Journal of Surgery 2012
Chapter 3

Abstract

Background

Decisions on local and systemic wound treatment vary among surgeons and are frequently based on expert opinion. The aim of this meta-review was to compile best available evidence from systematic reviews in order to formulate conclusions to support evidence-based decisions in clinical practice.

Methods

All Cochrane systematic reviews (CSRs), published by the Cochrane Wounds and Peripheral Vascular Diseases Groups, and that investigated therapeutic and preventive interventions, were searched in the Cochrane Database up to June 2011. Two investigators independently categorized each intervention into five levels of evidence of effect, based on size and homogeneity, and the effect size of the outcomes.

Results

After screening 149 CSRs, 44 relevant reviews were included. These contained 109 evidence-based conclusions: 30 on venous ulcers, 30 on acute wounds, 15 on pressure ulcers, 14 on diabetic ulcers, 12 on arterial ulcers and eight on miscellaneous chronic wounds. Strong conclusions could be drawn regarding the effectiveness of: therapeutic ultrasonography, mattresses, cleansing methods, closure of surgical wounds, honey, antibiotic prophylaxis, compression, lidocaine – prilocaine cream, skin grafting, antiseptics, pentoxifylline, debridement, hyperbaric oxygen therapy, granulocyte colony-stimulating factors, prostanoids and spinal cord stimulation.

Conclusion

For some wound care interventions, robust evidence exists upon which clinical decisions should be based.
Introduction

Many healthcare professionals are involved in the treatment and prevention of acute or chronic wounds. Decisions are made daily that affect wound healing, pain and costs. Acute and chronic wounds form a substantial problem in different healthcare settings: emergency departments, nursing homes, home care and family practices. Approximately €30 million is spent on (local) wound care in the Netherlands, and in the UK the costs of wound care in 2005 – 2006 were estimated to be between £15 and £18 million (European Wound Management Association and A. Nelson, personal communication). Because wounds have a considerable impact on patient morbidity, mortality, daily functioning and quality of life, they deserve high-quality local and systemic treatment.

Ideally, treatment decisions concerning these wounds should be based on the best available evidence, integrated with patients’ concerns and priorities, and accounting for the local situation, resources and skills. In reality, however, treatment decisions are generally based on personal opinion, experience and the preference of healthcare professionals. This is due partly to the overwhelming amount of literature available, which often shows conflicting results.

Although the total body of evidence concerning wound care is substantial, high-level evidence to guide decisions on treatment, such as meta-analyses and randomized clinical trials (RCTs), is relatively scarce. Nevertheless, the best available evidence should be identified and applied to decisions in daily practice.

This meta-review of Cochrane systematic reviews (CSRs) was conducted for both local and systemic treatment options for open wounds to assist healthcare professionals involved in wound care.

Methods

Searching and selecting

For this meta-review, all CSRs on local and systemic wound care were included, because these are considered the highest level of evidence for effectiveness of treatments in the hierarchy of study designs. Eligible CSRs dealt with the treatment or prevention of open wounds of any type and aetiology, in adults as well as in children. Reviews on prevention of surgical-site infection were excluded because these primarily comprise closed wounds.
Chapter 3

All systematic reviews in the Cochrane Database of Systematic Reviews up to June 2011, as published by the Cochrane Wounds Group and the Cochrane Peripheral Vascular Diseases Group, were retrieved and screened independently by two researchers, and by a third in case of any disagreement.

Appraising the strength of evidence

Because all CSRs undergo clinical and methodological scrutiny, formal appraisal of their internal validity was not needed. Instead, two researchers independently classified each CSR into one of five levels of evidence of effect (Table 1). For this classification, each prevention or treatment comparison and outcome was graded by taking into account the number of trials and participants included, consistency of results, and potential for pooling of the results. In the case of apparent methodological flaws or contradictory results in the individual trials, the level of evidence of the intervention studied was downgraded. A third arbiter resolved any disagreement. If the outcome did not show strong evidence of effect (level 5), a more tentative conclusion was given if the majority of the trials showed consistent results towards a positive or negative effect.

To check the robustness of the classification, a sensitivity analysis was performed by applying different definitions of a large study population, referring to the total number of patients available for each treatment per comparison. By default, large was defined as comprising at least 100 patients, because this number was representative of larger studies in the included CSRs.

Table 1. Definition of categories to grade the strength of evidence effect

<table>
<thead>
<tr>
<th>Levels of evidence of effect</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Strong evidence of effect</td>
<td>Significant results in favour of new treatment, based on pooled data of trials totalling &gt;100 patients</td>
</tr>
<tr>
<td>2. Strong evidence of no effect</td>
<td>Significant results in favour of control treatment or non-significant differences, based on pooled data of studies totalling &gt;100 patients</td>
</tr>
<tr>
<td>3. Limited evidence of effect</td>
<td>Significant results in favour of new treatment, based on one or more large (&gt;100 patients) but unpoolable studies or pooled results from small studies totalling &lt;100 patients</td>
</tr>
<tr>
<td>4. Limited evidence of no effect</td>
<td>Significant results in favour of control treatment or non-significant difference, based on one or more large (&gt;100 patients) but unpoolable studies or pooled results from small studies totalling &lt;100 patients.</td>
</tr>
<tr>
<td>5. Neither strong nor limited evidence of effect</td>
<td>No large or poolable trials available. These small trials may show: a) Significantly positive treatment effect (++) b) Trend towards positive treatment effect (+) c) No significant differences (0) d) Trend towards negative treatment effect (-) e) Significantly negative treatment effect (-)</td>
</tr>
</tbody>
</table>
Extracting and presenting data

Data were extracted by two researchers and checked by a third for interventions, comparisons and outcome as reported by the authors of the CSRs. Subsequently, the CSRs were grouped into those addressing local, systemic or preventive measures for the various wound types, acute and chronic wounds. When a CSR covered two or more wound types, for example miscellaneous chronic wounds and diabetic ulcers, only the relevant parts of the same review were included in the category.

Traumatic and surgical wounds were classified as acute wounds. Chronic wounds were defined as those characterized by delayed healing despite comprehensive re-evaluation and appropriate adjustment of treatment. Examples of chronic wounds are pressure ulcers, arterial or venous leg ulcers, and diabetic foot ulcers.

Results

After screening 68 and 82 abstracts from the Cochrane Wounds Group and the Cochrane Peripheral Vascular Disease Group, 41 and three relevant CSRs respectively were identified. Not all therapeutic or preventive measures in these 44 CSRs reflected first-choice clinical treatment options. The present conclusions therefore discuss treatment options as described by CSRs, despite their position as first, second or last resort choice, and clinical relevance.

From the 44 CSRs, there were 52 reviews of different wound types from which evidence-based conclusions could be extracted. Thirteen of these addressed acute wounds, and the remaining 39 addressed chronic wounds: 14 venous ulcers, eight pressure ulcers, seven diabetic ulcers, five arterial ulcers and five miscellaneous chronic wounds. The acute wounds contained surgical incisions, traumatic lacerations, surgical (infected) wounds and burns. Owing to the limited number of CSRs dealing with various acute wounds, these results are reported as a single category.

A total of 33 conclusions with strong evidence of effect and 18 conclusions with fairly strong evidence of effect could be drawn from the CSRs, whereas evidence was not available or insufficient in the remaining 58. The majority (79 of 109, 72.5 per cent) of the conclusions referred to chronic wounds. The conclusions based on the evidence found in the CSRs were divided into preventive, systemic and local treatments. The strongest conclusions are summarized as recommendations (Table 8).
Sensitivity analysis

To assess a possible effect on the results, the number of strong, fairly strong and weaker levels of evidence were recalculated using \( n = 40, n = 60, n = 80 \) and \( n = 120 \) as alternative definitions of a large study population. The number of strong recommendations (level 1 and 2) did not change substantially until a patient population of 60 or fewer was used. Hence, the validity the proposed 100-patient threshold was considered sufficient.

Acute wounds (Table 2)

Preventive systemic treatment in the form of prophylactic antibiotics proved to be ineffective in preventing infection after dog bites, with the exception of human and dog

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of last update review</th>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Evidence by reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al.</td>
<td>2010</td>
<td>Water for wound cleansing</td>
<td>2</td>
<td>No difference between drinkable tap water or other solution to cleanse wounds to prevent wound infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>5c</td>
</tr>
<tr>
<td>Coulthard et al.</td>
<td>2009</td>
<td>Tissue adhesives for closure of surgical incisions excluding high-tension areas</td>
<td>2</td>
<td>No difference between sutures, adhesive tape and tissue adhesives for wound healing</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5d</td>
</tr>
<tr>
<td>Farion et al.</td>
<td>2007</td>
<td>Tissue adhesives for traumatic lacerations in children and adults</td>
<td>1</td>
<td>Tissue adhesives are a reasonable alternative to close traumatic lacerations, despite a slightly increased rate of wound dehiscence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Jull et al.</td>
<td>2008</td>
<td>Honey as a topical treatment for wounds</td>
<td>1</td>
<td>Honey improves healing time in moderate superficial and partial thickness burns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5d</td>
</tr>
<tr>
<td>Wasiak et al.</td>
<td>2008</td>
<td>Dressings for superficial and partial-thickness burns</td>
<td>5a</td>
<td>Biosynthetic and hydrocolloid dressings may reduce wound healing time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5c</td>
</tr>
</tbody>
</table>
### Local and Systemic Wound Care

**Vermeulen et al.** 2003

**Dressings and topical agents for surgical wounds healing by secondary intention**

- NG: No evidence to support the effectiveness of foam, alginate, hydrocolloid or bead dressing
- 3: Gauze therapy could lead to greater discomfort but lower costs
- 5a: Plaster cast may reduce healing time compared with elastic compression
- 5d: Aloe vera may delay wound healing compared with gauze

**Wasiak and Cleland** 2010

**TNP for partial-thickness burns**

- 5b: A reduction in burn size at day 5 was seen when TNP was compared with SDD

**Dryburh et al.** 2011

**Debridement for surgical wounds**

- 5c: Insufficient evidence for the effectiveness of debridement alone or the choice of different methods to achieve a clean wound bed
- 5b: Controversial evidence concerning dextranomer, but could reduce the time to a clean wound bed when using enzymatic agent

### Systemic Care

**O’Mathuna and Ashford** 2010

**Therapeutic touch for healing acute wounds**

- 2: No effect of therapeutic touch for healing of wounds after minor surgery

**Eskes et al.** 2010

**HBOT for acute surgical and traumatic wounds**

- 5a: HBOT may increase complete wound healing in crush injuries compared with sham HBOT

### Prevention

**Medeiros and Saconato** 2001

**Antibiotic prophylaxis for mammalian bites**

- 2: Strong evidence that prophylactic antibiotics for dog bites do not prevent infection
- 1: Expect when the bite wound is located on the hand
- 5a: Prophylactic antibiotics after bites of humans may prevent infection

**Lethaby et al.** 2008

**Pin-site care for preventing infections associated with external bone fixators and pins**

- 2: Cleansing versus no cleansing showed no difference in infection rate
- 5c: Saline versus alcohol or frequency of cleansing showed no difference
- 5b: Xeroform treatment versus other dressings may reduce the incidence of infection

**Storm-Versloot et al.** 2010

**Topical silver for preventing wound infection**

- 3: Contradictory limited evidence of increased infection and
- 4: Decreased infection rates when using SSD cream
- 5c: No evidence for effectiveness of topical silver for preventing wound infection in terms of wound healing and wound infection

SSG, superficial skin grafts; TNP, topical negative pressure; SSD, silver sulfadiazine; HBOT, hyperbaric oxygen therapy
bites located on hands.\textsuperscript{27} Availability of antibiotics and familiarity with their use should lead to the implementation of this preventive option in clinical care.

There is strong evidence that systemic treatment with therapeutic touch does not have any additional effect on wound healing compared with placebo or non-treatment after minor surgery.\textsuperscript{25} Cleansing of pin-site wounds associated with orthopaedic fixators using saline, alcohol, hydrogen peroxide or antibacterial soap to prevent infections was not effective when compared with no cleansing.\textsuperscript{28}

For the local care of burn wounds, the effectiveness on wound healing of topical negative pressure compared with silver sulfadiazine remains unclear, owing to insufficient evidence.\textsuperscript{23} For burn wounds the use of silver sulfadiazine should be discouraged, as several trials showed a trend towards wound healing delay and increased pain and infection rates.\textsuperscript{21,29} Conversely, topical honey was strongly proven to reduce wound healing time compared with film or gauze-based dressings for burn wounds.\textsuperscript{20}

If acute wounds, such as lacerations or soft tissue wounds, need cleansing, the use of drinkable tap water is strongly effective in reducing wound infections compared with saline solutions.\textsuperscript{17} For closing traumatic lacerations, tissue adhesives compared with standard wound care were strongly effective.\textsuperscript{19} Despite a slightly increased rate of wound dehiscence and higher cost, tissue adhesives can be considered a reasonable alternative.\textsuperscript{19} This seems particularly relevant as the improved cosmetic outcome is gaining in importance.\textsuperscript{18,19}

**Venous ulcers (Table 3)**

No trials were found comparing compression therapy with no compression to prevent recurrence of healed venous leg ulcers.\textsuperscript{42}

The following systemic treatment options are available when first-choice options fail, and should be considered alongside patient preferences, costs and wound type. For instance, pentoxifylline was strongly effective in promoting wound healing compared with placebo, in combination with compression therapy.\textsuperscript{39} This was true for people of all ages with a venous ulcer and in any care setting, with a duration varying from 4 to 26 months.\textsuperscript{39} Despite controversy about its clinical indications, pentoxifylline is an inexpensive drug with few side-effects and a number needed to treat (NNT) of four patients to improve wound healing significantly.

One small trial, in which 18 venous ulcers were included with treatment failure for over 1 year, did not provide sufficient evidence on the effectiveness of hyperbaric oxygen therapy (HBOT) versus sham therapy.\textsuperscript{41} Oral zinc was strongly ineffective for ulcer
# Table 3: Treatment recommendations for venous ulcers based on the grading system (Table 1)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of last update review</th>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Evidence by reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Meara et al.</td>
<td>2008</td>
<td>Compression for venous leg ulcers</td>
<td>1</td>
<td>Elastic compression improves wound healing more than inelastic compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 High compression improves wound healing more than low compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 Multilayered compression could improve wound healing more than single-layered compression and there seems no difference between the effect of two- and four-layer compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5a Compression may increase ulcer healing rates more than no compression</td>
</tr>
<tr>
<td>Palfreyman et al.</td>
<td>2006</td>
<td>Dressings for healing venous leg ulcers</td>
<td>2</td>
<td>Type of wound dressing beneath compression does not influence healing (trials included hydrocolloids, foam dressings, alginates, low-adherent dressings and hydrogels)</td>
</tr>
<tr>
<td>Briggs and Nelson</td>
<td>2010</td>
<td>Topical agents or dressings for pain in venous leg ulcers</td>
<td>1</td>
<td>Lidocaine – prilocaine cream decreases pain during ulcer debridement (not clear whether this affects healing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 Ibuprofen slow-release foam dressing has no effect on pain relief</td>
</tr>
<tr>
<td>Jones and Nelson</td>
<td>2009</td>
<td>Skin grafting for venous leg ulcers</td>
<td>1</td>
<td>Bilayer artificial skin increases the proportion of ulcer healing more than standard care</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 Single-layer skin replacement probably does not improve healing rates more than standard care</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 Allografting seems to improve healing rates more than standard care</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5a Pinch grafts may increase ulcer healing more than xenografts</td>
</tr>
<tr>
<td>Al-Kurdi et al.</td>
<td>2010</td>
<td>Therapeutic ultrasound for venous leg ulcers</td>
<td>3</td>
<td>Therapeutic ultrasound could decrease ulcer area</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 No difference between therapeutic ultrasound and sham treatment in ulcer healing</td>
</tr>
<tr>
<td>O’Meara et al.</td>
<td>2010</td>
<td>Antibiotics and antiseptics for venous ulcers</td>
<td>1</td>
<td>Cadexomer iodine increases ulcer healing compared with standard care both with, and without compression therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 Ethacridine lotion added to compression could reduce ulcer area by 20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5c Contradictory results for ulcer healing concerning povidone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5b Peroxide 10% could support area reduction of venous leg ulcers</td>
</tr>
<tr>
<td>Nelson et al.</td>
<td>2011</td>
<td>IPC for venous leg ulcers</td>
<td>2</td>
<td>IPC with compression does not contribute to ulcer healing compared with compression treatment alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5a IPC with dressing versus dressing alone may have a positive effect on ulcer healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5b Rapid IPC may improve ulcer healing more than slow IPC</td>
</tr>
</tbody>
</table>
healing compared with placebo. None of the 25 trials comparing the routine use of antibiotics and antiseptics with standard care, other antibiotics or placebo provided strong or consistent fairly strong evidence on quicker wound healing. Therefore, no antimicrobial drug should be used without evidence of colonization or infection.

For local treatment, skin grafting compared with standard care was not effective for venous ulcer healing, except for bilayer artificial skin treatment of ‘hard to heal’ ulcers. The high cost of this treatment is an important factor to consider when interpreting these results.

Laser therapy showed limited evidence of effect compared with sham or (infra)red light, and electromagnetic therapy showed insufficient evidence of effect compared with sham or standard therapy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of last update review</th>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Evidence by reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flemming and Cullum</td>
<td>2011</td>
<td>Laser therapy for venous leg ulcers</td>
<td>4</td>
<td>No difference in wound healing between laser therapy and sham therapy</td>
</tr>
<tr>
<td>Aziz et al.</td>
<td>2011</td>
<td>Electromagnetic therapy for venous leg ulcers</td>
<td>5c</td>
<td>Insufficient evidence for the effectiveness of electromagnetic therapy on ulcer healing</td>
</tr>
<tr>
<td>Systemic care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jull et al.</td>
<td>2010</td>
<td>Pentoxifylline for venous leg ulcers</td>
<td>1</td>
<td>Pentoxifylline increases ulcer healing with, or without compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 More adverse (mainly gastrointestinal) events occur during pentoxifylline treatment</td>
</tr>
<tr>
<td>Wilkinson and Hawke</td>
<td>2010</td>
<td>Oral zinc for arterial and venous leg ulcers</td>
<td>2</td>
<td>Oral zinc has no effect on ulcer healing</td>
</tr>
<tr>
<td>Kranke et al.</td>
<td>2003</td>
<td>HBOT for chronic wounds</td>
<td>5b</td>
<td>Insufficient evidence for effectiveness of HBOT on healing</td>
</tr>
<tr>
<td>O’Meara et al.</td>
<td>2010</td>
<td>Antibiotics and antiseptics for venous leg ulcers</td>
<td>4</td>
<td>No difference in healing between ciprofloxacin and standard care</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5c Insufficient evidence for effectiveness of routine use of antibiotics to promote healing</td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson et al.</td>
<td>2000</td>
<td>Compression for preventing recurrence of venous ulcers</td>
<td>5c</td>
<td>No trials found comparing compression versus no compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5b High compression may lead to fewer recurrences</td>
</tr>
</tbody>
</table>

IPC, intermittent pneumatic compression; HBOT, hyperbaric oxygen therapy.
Strong evidence of effect was shown for high compression versus low compression, whereas elastic bandages were more effective than inelastic bandages. Limited evidence of effect was shown when comparing multicomponent and single-component systems. Seven small trials showed significantly positive effects in terms of quicker ulcer healing when comparing compression therapy, as either bandages or pneumatic devices, with no compression therapy. A simple, comfortable local dressing, such as low-adherent knitted viscose, can be used beneath compression bandages, as there was strong evidence that no dressing type had an additional beneficial effect over any other.

For sharp debridement, there was strong evidence that a eutectic mixture of local anaesthetic (lidocaine – prilocaine), as opposed to placebo, provided effective pain relief (although the impact of debridement on healing was unclear and lidocaine – prilocaine is not licensed for use in open wounds in all settings). In contrast, there was strong evidence of no effect on pain relief for ibuprofen slow-release foam dressing compared with other foam dressings.

Limited evidence of effect is available for the following local antimicrobial therapies in addition to compression therapy to increase healing rates: slow-release iodine, cadexomer, compared with standard care or hydrocolloid, and ethacridine lotion 0.1 per cent versus placebo. Systemic side-effects from the potential absorption of iodine should be considered when using iodine for the treatment of wounds. Ethacridine lotion is seldom used in practice as a wound disinfectant; this could be due to poor accessibility.

**Diabetic ulcers (Table 4)**

For the prevention of diabetic ulcers, patient education, as opposed to usual care or brief education, had limited effectiveness in developing foot care knowledge and behaviour that might decrease the incidence of subsequent ulceration or amputation. Pressure-relieving interventions, such as orthotic devices or therapeutic shoes, tend to reduce the incidence of ulceration and callus formation compared with standard therapy, although there was insufficient evidence to draw a strong conclusion.

Systemic additional treatment with HBOT, as opposed to sham or control treatment, is strongly effective in decreasing major amputations, with a NNT of four patients. There is insufficient evidence that systemic treatment with granulocyte-colony-stimulating factor (G-CSF) can help cure infections or heal ulcers. On the other hand, G-CSF, compared with standard care, had limited effectiveness in decreasing the need for surgical intervention, especially amputation. However, the small therapeutic bandwidth and high costs mean that this therapy should not be used as a first treatment option, but only when other treatment options fail.
There is strong evidence of benefit for the local application of hydrogels after debridement compared with standard treatment after debridement, gauze-based dressings or standard treatment. Table 4 presents the treatment recommendations for diabetic ulcers based on the grading system (Table 1).

### Table 4 Treatment recommendations for diabetic ulcers based on the grading system (Table 1)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of last update review</th>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Evidence by reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edwards and Stapely</td>
<td>2009</td>
<td>Debridement for diabetic foot ulcers</td>
<td>1</td>
<td>Strong evidence for effectiveness of hydrogel on healing rate of diabetic foot ulcers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1          Fewer complications occur when using hydrogel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5b         Surgical or larval debridement may decrease healing time compared with conventional treatment or hydrogel</td>
</tr>
<tr>
<td>Bergin and Wraight</td>
<td>2010</td>
<td>Silver-based wound dressings and topical agents for treating diabetic foot ulcers</td>
<td>5c</td>
<td>No eligible studies identified so no evidence for effectiveness of silver-based wound dressings</td>
</tr>
<tr>
<td>Spencer</td>
<td>2000</td>
<td>Pressure-relieving interventions for preventing and treating diabetic foot ulcers</td>
<td>5a</td>
<td>Total contact casts in treatment of diabetic foot ulcers may be effective</td>
</tr>
<tr>
<td><strong>Systemic care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranke et al.</td>
<td>2003</td>
<td>HBOT for chronic wounds</td>
<td>1</td>
<td>HBOT decreases the risk of major amputation versus control treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5b          Difference in healing after 1 year was seen in contrast to results directly after HBOT</td>
</tr>
<tr>
<td>Cruciani et al.</td>
<td>2011</td>
<td>G-CSF as adjunctive therapy for diabetic foot infections</td>
<td>3</td>
<td>G-CSF could decrease the need for surgical intervention, especially amputation, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5b          duration of hospitalization may be effective, especially in life-threatening infection</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorresteijn et al.</td>
<td>2010</td>
<td>Patient education for preventing diabetic foot ulceration</td>
<td>3</td>
<td>Limited evidence of effectiveness for patient education on foot care knowledge and behaviour</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5c          Incidence of foot ulceration did not differ in the trials</td>
</tr>
<tr>
<td>Spencer</td>
<td>2000</td>
<td>Pressure-relieving interventions for preventing and treating diabetic foot ulcers</td>
<td>5a</td>
<td>Manufactured shoes may help to reduce the incidence of ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5b          Orthotic interventions tended to result in less callus formation after 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5a          Significantly more callus resolution than with standard podiatry</td>
</tr>
</tbody>
</table>

HBOT, hyperbaric oxygen therapy; G-CSF, granulocyte-colony-stimulating factor.
care to promote wound healing. There is a lack of relevant trials comparing silver-based wound dressings in diabetic foot ulcers. Evidence on the effectiveness of total costs as pressure-relieving treatment is very limited.

**Arterial ulcers (Table 5)**

No evidence-based conclusions can be drawn concerning preventive actions.

Systemic treatment with prostanoids compared with placebo in patients with critical leg ischemia (CLI) was shown to be strongly effective in relieving rest pain and improving ulcer healing, but had no clear effect on late amputation rates. Prostanoids can be considered a last-resort treatment option because of the high costs and the fact that the dose has to be increased until side-effects appear in order to obtain maximum treatment effect.

**Table 5** Treatment recommendations for arterial ulcers based on the grading system (Table 1)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of last update review</th>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Evidence by reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson and Bradley</td>
<td>2006</td>
<td>Dressings and topical agents</td>
<td>5c</td>
<td>Insufficient evidence for ulcer healing or area reduction for any dressing or topical agent for arterial leg ulcers</td>
</tr>
<tr>
<td>Systemic care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilkinson and Hawke</td>
<td>2010</td>
<td>Oral zinc for treating ulcers</td>
<td>5b</td>
<td>Oral zinc may increase healing of arterial and venous leg ulcers</td>
</tr>
<tr>
<td>Ruffolo et al.</td>
<td>2009</td>
<td>Prostanoids for CLI</td>
<td>2</td>
<td>No effect for long-term effectiveness and safety in patients with CLI, despite</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Ubbink and Vermeulen</td>
<td>2008</td>
<td>SCS for NR-CCLI</td>
<td>1</td>
<td>SCS improves limb salvage and clinical situations in patients with NR-CCLI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5a</td>
</tr>
<tr>
<td>Fowkes and Leng</td>
<td>2007</td>
<td>Bypass surgery for chronic lower limb ischaemia</td>
<td>3</td>
<td>Compared with thrombolysis, surgery could result in fewer amputations and has a lower incidence of ongoing or recurrent ischaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5c</td>
</tr>
</tbody>
</table>

CLI, critical limb ischaemia; SCS, spinal cord stimulation; NR-CCLI, non-reconstructable chronic critical leg ischaemia; PTA, percutaneous transluminal angioplasty.
For patients with CLI, the focus is often on limb salvage rather than ulcer healing. Spinal cord stimulation (SCS) for the treatment of non-reconstructable CLI showed strong evidence of effectiveness, and resulted in an improved limb salvage rate, compared with findings in patients treated conservatively. On the other hand, costs, patient selection and experience with the treatment need to be taken into account when considering treatment with SCS. Bypass surgery showed evidence of effectiveness, albeit limited, in the prevention (or postponement) of major amputation, but other outcomes did not differ significantly from exercise or SCS in patients with CLI.

Lack of available trials preclude any evidence-based conclusions to be drawn on which local topical agents or dressings should be used for the healing of arterial ulcers.

**Pressure ulcers (Table 6)**

Strong evidence for the effectiveness of high-specification foam mattresses (contoured-foam support surfaces comprising foam of different densities) and limited evidence for low air-loss mattresses was found over standard hospital foam mattresses and standard beds for prevention of pressure ulcers. In one large trial, limited evidence was found for a mixed nutritional supplement diet to reduce the development of pressure ulcers more than a standard hospital diet.

No conclusions from available Cochrane evidence can be made regarding the effectiveness of systemic treatments. Regarding local treatments, there is strong evidence that therapeutic ultrasound is ineffective compared with sham ultrasound, with ulcer healing as the main outcome. The possible positive effect on ulcer healing of electromagnetic therapy remains unproven, as only two small trials have been performed, with no convincing evidence for effectiveness. Furthermore, no particular wound cleansing solution or technique has shown any substantial effect on ulcer healing.

**Miscellaneous chronic wounds (Table 7)**

Insufficient evidence is available for the use of topical silver for the treatment of infected or contaminated wounds. A trend towards a positive effect on healing time was seen in a small trial of honey at the cost of more adverse events in comparison with Edinburgh University Solution of Lime (EUSOL).

No evidence-based conclusions for systemic treatments can be drawn.
### Table 6: Treatment recommendations for pressure ulcers based on the grading system (Table 1)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of last update review</th>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Evidence by reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baba-Akbari Sari et al.(^{51})</td>
<td>2008</td>
<td>Therapeutic ultrasound for pressure ulcers</td>
<td>2</td>
<td>Strong evidence for ineffectiveness of therapeutic ultrasound for ulcer healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5c</td>
<td>Ultrasound versus laser did not show a difference in ulcer healing</td>
</tr>
<tr>
<td>Aziz et al.(^{52})</td>
<td>2010</td>
<td>Electromagnetic therapy for treating pressure ulcers</td>
<td>5b</td>
<td>Small trials describe that electromagnetic therapy may be effective for ulcer healing</td>
</tr>
<tr>
<td>Moore and Cowman(^{53})</td>
<td>2010</td>
<td>Wound cleansing for pressure ulcers</td>
<td>5c</td>
<td>No trials found comparing cleansing versus no cleansing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5d</td>
<td>Saline versus water cleansing, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5d</td>
<td>whirlpool versus no whirlpool cleansing technique may be less effective in terms of ulcer healing</td>
</tr>
<tr>
<td><strong>Systemic care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Langer et al.(^{54})</td>
<td>2003</td>
<td>Nutritional interventions for preventing and treating pressure ulcers</td>
<td>5b</td>
<td>Small trials show no difference when adding ascorbic acid supplementation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5c</td>
<td>High-protein diet reported contradictory results for ulcer healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5d</td>
<td>Zinc supplementation may be ineffective for prevention of pressure ulcers</td>
</tr>
<tr>
<td>Moore and Cowman(^{55})</td>
<td>2008</td>
<td>Repositioning for treating pressure ulcers</td>
<td>5c</td>
<td>No trials found on this subject</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McInnes et al.(^{56})</td>
<td>2010</td>
<td>Support surfaces for pressure ulcer prevention</td>
<td>1</td>
<td>High-specification foam mattresses better than standard hospital foam mattresses to prevent ulcers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>No difference in effectiveness of alternating-pressure and constant low-pressure mattresses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>Pressure-relieving overlays on operating table are effective in prevention of postoperative pressure ulcers</td>
</tr>
<tr>
<td>Moore and Cowman(^{57})</td>
<td>2010</td>
<td>Risk assessment tools for prevention of pressure ulcers</td>
<td>5c</td>
<td>One underpowered trial showed no difference when Braden risk assessment tool and training was compared with unstructured risk assessment and training or unstructured risk assessment alone</td>
</tr>
<tr>
<td>Langer et al.(^{54})</td>
<td>2003</td>
<td>Nutritional intervention for prevention of pressure ulcers</td>
<td>3</td>
<td>Mixed diet reduced development of pressure ulcers versus hospital diet</td>
</tr>
</tbody>
</table>
**Discussion**

Useful conclusions can be drawn from CSRs to support evidence-based decisions in wound care. They mostly involve the care of patients with chronic or venous leg ulcers, and are thus relevant to a range of healthcare professionals. The conclusions presented here are of the highest level available and healthcare professionals involved in wound care should be aware of them (Table 8).

**Table 7** Treatment recommendations for miscellaneous chronic wounds based on the grading system (Table 1)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of last update review</th>
<th>Intervention</th>
<th>Level of evidence</th>
<th>Evidence by reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jull et al. 20</td>
<td>2008</td>
<td>Honey as topical treatment for wounds</td>
<td>5a</td>
<td>Shorter healing time for honey treatment compared with EUSOL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5e</td>
<td>More adverse events reported in the honey-treated groups compared with other wound dressings</td>
</tr>
<tr>
<td>Adderley and Smith</td>
<td>2011</td>
<td>Topical agents and dressings for fungating wounds</td>
<td>5c</td>
<td>Quality of life was not reported for any dressing or topical agent for managing wound symptoms associated with fungating wounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5a</td>
<td>Longer duration until treatment failure was seen for miltefosine 6%</td>
</tr>
<tr>
<td>Vermeulen et al. 60</td>
<td>2006</td>
<td>Topical silver for treating infected wounds</td>
<td>5c</td>
<td>Silver-containing dressings or topical agents for treatment of infected or contaminated chronic wounds may have no effect on wound healing</td>
</tr>
<tr>
<td>Systemic care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ubbink et al. 51</td>
<td>2007</td>
<td>TNP for treating chronic wounds</td>
<td>5b</td>
<td>Insufficient evidence for effectiveness of TNP in healing of chronic wounds, although there was a trend towards positive treatment effects in favour of TNP</td>
</tr>
<tr>
<td>Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storm-Versloot et al</td>
<td>2010</td>
<td>Topical silver for preventing wound infection</td>
<td>5c</td>
<td>Insufficient evidence for effectiveness of silver-containing dressings or topical agents to promote wound healing or prevent wound infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5d</td>
<td>Aquacel® Ag had a longer healing time and more infections compared with Algosteril®</td>
</tr>
</tbody>
</table>

EUSOL, Edinburgh University Solution of Lime; TNP, topical negative pressure.

Topical negative-pressure therapy was not shown to be effective for healing chronic wounds in seven small trials. Despite the absence of evidence from CSRs, topical negative-pressure therapy is frequently used in practice.61,62
Table 8 Summary of strong levels (1 and 2) of evidence and recommendations for wound care

<table>
<thead>
<tr>
<th>Wound type</th>
<th>Recommendation and effect size of the treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute wounds</strong></td>
<td></td>
</tr>
<tr>
<td>Mammalian bites(^{27})</td>
<td>Prevent infection with prophylactic antibiotics, particularly in hands; NNT 4 (3, 8)</td>
</tr>
<tr>
<td>Superficial and partial-thickness burns(^{30,29})</td>
<td>Apply local honey for quick healing, as WMD of 5 (−5.1, −4.3) days is reported compared with conventional dressings</td>
</tr>
<tr>
<td>Laceration and soft tissue wounds(^{17})</td>
<td>In acute wounds do not use silver sulfadiazine as topical agent; NNH 13 (7, 1667)</td>
</tr>
<tr>
<td><strong>Chronic wounds</strong></td>
<td></td>
</tr>
<tr>
<td>Venous ulcers(^{30,36,39})</td>
<td>Systemic treatment with pentoxifylline increases complete wound healing; NNT 4 (3, 7)</td>
</tr>
<tr>
<td>Diabetic ulcers(^{41,43})</td>
<td>Use hyperbaric oxygen therapy to decrease major amputation rate; NNT 5 (3, 12)</td>
</tr>
<tr>
<td>Arterial ulcers in patients with critical leg ischaemia(^{46,50})</td>
<td>Use systemic prostanoids in patients with critical leg ischaemia to relieve rest pain, NNT 11 (7, 28), and improve ulcer healing, NNT 9 (6, 17)</td>
</tr>
<tr>
<td>Pressure ulcers(^{51,56})</td>
<td>Use spinal cord stimulation to improve limb salvage; NNT 9 (5, 45)</td>
</tr>
<tr>
<td></td>
<td>Use high-specification foam mattresses, NNT 13 (10, 21), and low air-loss mattresses, NNT 5 (3, 9), to prevent pressure ulcers on the ward, and pressure-relieving overlays on the operating table; NNT 17 (10, 54)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95 per cent confidence intervals. NNT, number needed to treat; WMD, weighted mean difference; NNH, number needed to harm.

Obviously, the conclusions given here do not offer treatment solutions for every wound type, because strong evidence is not yet available for all situations. When systematic reviews do not present strong evidence or suggest that more research is needed, clinicians have to rely on practical and pragmatic advice given in consensus guidelines. Some of the present conclusions, such as compression therapy for venous ulcers, may seem obvious. However, the availability of such strong evidence turns best practice into evidence-based practice. Other recommendations may be contrary to common practice or counterintuitive, such as the lack of evidence for silver dressings or negative-pressure therapy for certain types of wound. This may imply that current practice is not evidence-based and needs to change in order to ensure best quality care. Another example is pentoxifylline. Despite the strong evidence available regarding its effectiveness for venous ulcers, it is seldom used in clinical practice. Clinicians are not familiar with this drug and the manufacturer is reluctant to change its advice on the indications for pentoxifylline. Nevertheless, modern caregivers are compelled to offer their patients...
best available care with proven effectiveness. The medical profession is changing rapidly, and all too often new evidence emerges that contradicts standard routines; yet it can take a considerable time to be implemented and for the old routine to be abolished.\textsuperscript{63} Some treatment practices, for which strong evidence is lacking, may still be warranted by other, lower levels of evidence not presented here. Sometimes, when evidence is lacking, choices need to be made based on personal or peer expertise, which is still in agreement with evidence-based practice. Besides, some conclusions made in this meta-review belong to the last-resort options of the therapeutic ladder.

Furthermore, lack of evidence of benefit is not the same as evidence of lack of benefit. Hence, the absence of robust evidence of effectiveness does not exclude a potentially beneficial effect. Research in the form of large RCTs is needed to identify whether any benefit actually exists.

The 44 CSRs with firm conclusions show that a body of knowledge exists in the area of wound care. However, only one-third of these recommendations are strong and based on high-quality evidence. This confirms the disappointing overall level of evidence available in wound care, as already noted by others.\textsuperscript{13–15} This could be due to the fact that wound care products merely require trials to demonstrate safety and performance in order to obtain CE (Conformité Européene) marking, a persistent reluctance to perform high-quality research in wound care, the profitable and unrestricted market for new wound products without corresponding evidence, or the relentless power of case reports and personal opinion. Nevertheless, convincing evidence currently available about wound care should be used by all healthcare professionals and should therefore be readily accessible. This could help more effective, comprehensive and coherent wound care to be organized in the future.

There were limitations to the present study. First, only Cochrane reviews were included in this meta-review, and the omission of other systematic reviews or primary studies may have resulted in underrepresentation of the available evidence on certain types of wound care. Nevertheless, CSRs are considered the highest level of evidence in the hierarchy of study designs and are likely to correspond with other systematic reviews.\textsuperscript{16} Conclusions in the present review were based on effectiveness rather than the (overall) effect sizes found in the reviews. For this information, the reader is referred to the particular Cochrane reviews.

Second, the classification system of the evidence used here combined elements of different grading methods in order to summarize the broad topic of both local and systemic wound care. As no validated grading system exists as yet, key elements of Grading of Recommendations Assessment, Development and Evaluation (GRADE)\textsuperscript{63}
and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)\textsuperscript{64} guidelines were combined in this meta-review in order to evaluate levels of evidence of effect. The original instruments did not suffice, because these grading systems lean upon the original trials.

Third, the majority (72.5 per cent) of the conclusions referred to chronic wounds, especially venous ulcers (30 of the 79 conclusions for chronic wounds). This shows the existing niches in treatment choice, whereas some important questions, mainly concerning acute wounds, have not yet been addressed. New research should therefore stem from clinical dilemmas rather than the researchers’ or manufacturers’ interest.

Evidence-based medicine has developed into a lasting need rather than a passing fad for wound care practice.\textsuperscript{13,65} This overview of systematic reviews can contribute to effective wound care management. When gaps in knowledge or best practice exist, an analysis of consensus documents may offer pragmatic and practical advice until adequate scientific clinical research provides the missing answers.

**Acknowledgements**

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64. PRISMA. The PRISMA Statement. 2009; Available at http://www.prisma-statement.org/statement.htm [accessed 12-7-2013].

Chapter 4

Fundamentals of randomized clinical trials in wound care: design and conduct

A.M. Eskes
F.E. Bröllmann
B.E. Sumpio
D. Mayer
Z. Moore
M.S. Ågren
M. Hermans
K. Cutting
D.A. Legemate
D.T. Ubbink
H. Vermeulen

Wound Repair and Regeneration 2012
Chapter 4

Abstract

The care for chronic and acute wounds is a substantial problem around the world. This has led to a plethora of products to accelerate healing. Unfortunately, the quality of studies evaluating the efficacy of such wound care products is frequently low. Randomized clinical trials are universally acknowledged as the study design of choice for comparing treatment effects, as they eliminate several sources of bias. We propose a framework for the design and conduct of future randomized clinical trials that will offer strong scientific evidence for the effectiveness of wound care interventions. While randomization is a necessary feature of a robust comparative study, it is not sufficient to ensure a study at low risk of bias. Randomized clinical trials should also ensure adequate allocation concealment and blinding of outcome assessors, apply intention-to-treat analysis, and use patient-oriented outcomes. This article proposes strategies for improving the evidence base for wound care decision-making.
Introduction

Evaluation of wound care procedures and products is a challenge for researchers and clinicians alike. Unfortunately, only few articles are based on randomized clinical trials (RCTs). This article provides a guide for designing and conducting high-quality research focusing on, and relevant to, clinical practice. Based on a clinical scenario we will lead you through various issues related to RCTs.

Clinical scenario

You, a vascular surgeon, performed a below-knee amputation in a 70-year-old man suffering from an acute Charcot foot with an extensive infection of the plantar fascia originating from a neuropathic foot ulcer. Although you administered prophylactic antibiotics, the patient develops an infection at the amputation stump. Hence, you remove most of the stitches to drain the wound.

The wound care nurse discusses with you whether or not to apply an iodine dressing or another antiseptic agent locally. As an evidence-based surgeon, you search the evidence that would support a choice. Three comparative trials come close to the problem you are facing with this patient, but these do not address amputation wounds and show contradicting evidence about which antiseptic is to be preferred.1-3

Optimum study design

While treating your patient according to local best practice, you realize there is a need for an RCT to answer this clinical quandary. The first dilemma that immediately arises is: Which study design is preferable and feasible at the same time? RCTs are acknowledged by some as the methodologically preferable design for investigating treatment effects because they eradicate important sources of bias, such as selection and confounding bias.4-6 Any positive treatment effect found in an RCT generally provides more confidence about the efficacy of an intervention than in non-comparative studies or registries because possible confounders are equally distributed over the study groups, while known prognostic factors can be dealt with by stratification. This is advantageous particularly in wound care, where there is a large variety in types of wound, different wound aetiologies, multiple comorbidities, and a wide range of treatment options (e.g., for local and systemic wound care). A pragmatic, real-life study design, e.g., through liberal patient inclusion from various settings and accepting relevant co-interventions or common comorbidities, would yield information about effectiveness rather than mere efficacy of wound treatments.
Some argue that there is no sound reason for wound care researchers to choose a design other than an RCT to evaluate wound care strategies. Yet, RCTs are inappropriate in situations such as in case of rare, life-threatening diseases, such as toxic epidermal necrolysis, and when randomization would be unethical. It can be considered immoral to conduct an RCT to determine if primary amputation is as effective as a surgical or radiological intervention to treat critical leg ischemia. In such circumstances, data from observational studies may be more appropriate and sufficient.

A general, internationally accepted guideline on how to report RCTs has been formulated in the recently updated Consolidated Standards of Reporting Trials (CONSORT) statement. This statement is also, albeit indirectly, useful for the preparation and conduct of RCTs. In this article, we will elaborate on issues particularly relevant for the internal validity of RCTs in wound care.

**Study preparation**

In the clinical scenario presented above, an RCT to investigate the effectiveness of interventions seems possible and preferable. The next step is to consider several criteria that are considered essential components of intervention research (see Table 1). Formulating the exact research question helps define the patients needed for the study, the intervention under study, the standard policy as comparator, and the most clinically relevant outcomes.

Patients for whom the intervention is intended determine the setting from which eligible patients are to be selected, e.g., home care, general hospital, trauma or emergency ward, specialized wound clinic, nursing home, or university centre. The same holds true for the patient characteristics. To ensure the appropriate spectrum of patients, consider whether vulnerable patients due to the presence of comorbidities (e.g., diabetes, kidney failure requiring dialysis) or certain types of medication (e.g., steroids) should be excluded. These factors may reduce the clinical success rate and/or increase the rate of complications; on the other hand, the question arises whether the clinical success under these different conditions is of particular interest because it reflects real life. In amputees, diabetics may be an important patient group to include, whereas the use of steroids is a likely exclusion criterion as it seriously hampers the normal immune response.

Exclusion criteria will reduce the number of eligible patients. Keep in mind that narrow inclusion criteria, which should demonstrate more powerful treatment effects, lead to further difficulties in the recruitment of patients and the generalization of the results (external validity). Eligible patients should be fully informed about the treatment options...
and, if they decide to take part in the trial, they have to give written informed consent.\textsuperscript{10} Hence, it is advisable to perform an a priori sample size calculation (for more details, see section “Predefined plan for data analysis”) to achieve sufficient power to detect clinically relevant differences. Furthermore, this sample size provides a realistic estimate of the length of time needed to recruit patients.

To be able to include a sufficient number of patients within a reasonable time interval, one should consider increasing the number of recruiting centres. A multicentre trial is preferable, not only to accelerate recruitment but also to enhance the generalizability of the results.\textsuperscript{11} Admittedly, an (multicentre) RCT in wound care may be more time-consuming than a pharmaceutical study, at least in terms of the attending clinician’s time, and may subsequently interfere or disrupt daily practice routines. In addition, involving clinicians from different specialties in the trial will likely improve the implementation of the result.

### Table 1 Checklist of criteria to be defined and completed for an optimum design in wound care trials

<table>
<thead>
<tr>
<th>Setting</th>
<th>The trial setting (e.g. home care, general hospital, nursing home, or specialized (university) clinic) is defined</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Eligibility criteria for patients are described (inclusion and exclusion criteria)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Written informed consent will be obtained from every patient included</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Interventions</td>
<td>The treatment to apply in each trial arm is standardized</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Co-interventions are allowed but prespecified (the same in both trial groups)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary and secondary outcomes are prespecified</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>It is described when and how outcomes are assessed</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sample size</td>
<td>Sample size is calculated (calculation based on expected clinical relevant difference in primary endpoint)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Randomization</td>
<td>The unit of randomization defined (e.g., the wound or the patient)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>The allocation sequence is randomly generated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>The treatment allocation is adequately concealed</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blinding</td>
<td>It is defined who is blinded after assignment to the intervention and how, including:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Patients (recommend)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Caregivers (recommend)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Outcome assessors (strongly recommended)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td>All randomized patients are to be analyzed in the group to which they were allocated</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Funding</td>
<td>Funding through unrestricted grants only</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Duration of follow-up is defined</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ethics</td>
<td>Ethics review board approval</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Trial registration</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
of the trial by all invited specialties. Tissue viability nurses or specialized wound care nurses tend to be zealous in contributing to studies in their area of expertise and can therefore play an invaluable role. A drawback can be that multicentre RCTs are more expensive and pose logistic challenges, so financial support is a necessity to conduct a proper trial.

Generally, clinicians have had to rely ostensibly on financial support from commerce to extend the boundaries of our knowledge. In addition, the Food and Drug Administration (FDA) formulated some relevant patient outcomes for wound care (e.g., healing rate and pain relief) as the result of pharmaceutical interaction. Conversely, legislation in many countries does not consider wound care products as pharmaceutical agents, which may simplify the legal and safety requirements of such a trial. Ideally, first-choice funding should be obtained from independent (inter)national institutions. A second option is commercial funding from manufacturers to magnify valorisation of the knowledge obtained. Many of these manufacturers are relatively small and cannot afford lengthy and/or expensive studies, which calls for a joint effort by several stakeholders (e.g., wound care researchers, clinicians, manufacturers). To avoid any conflict of interest, analysis and reporting of the trial should remain the domain of the researchers. A legal agreement helps to ensure the grant is unrestricted. Unfortunately, there is a trend to publish only studies with positive results that favour the sponsoring industry. An “unrestricted grant” or a combination of sponsorships will assist in minimizing publication bias.

To demonstrate and document good clinical practice and patient safety, one should clearly describe the design of the RCT in sufficient detail in a research protocol. This protocol will need to undergo scrutiny by the local Ethics Review Board(s) before the study can start. In addition, one should register the research protocol in a publicly accessible database (http://www.isrctn.org or ClinicalTrials.gov) to announce the RCT is planned, ongoing, or completed. For many major medical journals this is a prerequisite for publication to reduce publication bias. Availability of a protocol can help to restrict post hoc changes to the methods during the inclusion period. Finally, a run-in period (e.g., pilot-inclusion of a few patients) can be useful to check the feasibility, logistics, and final success of the trial.

**Main methodological issues of design in RCT**

**Randomization and allocation concealment**

Randomization evenly distributes both known and unknown prognostic factors between comparison groups. In addition, one may stratify patients by factors known to influence
treatment outcomes, for example, age, wound size, and comorbidity, to disperse these demographic and prognostic factors evenly between the treatment groups. This even distribution ensures that detected differences are attributable only to the intervention under investigation and not to confounding variables. To detect any between-group differences, the collection and reporting of relevant patient and wound characteristics is essential (e.g., age, comorbidities, co-interventions, wound characteristics).

A concealed allocation process helps to reduce the risk of selection bias when comparison groups are not created in a truly random fashion. Examples are allocation by the person’s date of birth, by the day of the week, by a person’s medical record number, or just allocating every alternate person. These quasi-random methods do not offer patients an equal chance to receive either treatment. Furthermore, caregivers may easily become aware of the treatment the next patient will receive, which can cause (un)intentional inclusion or exclusion of the patient. Therefore, it is best to assign a person unrelated to the study to perform the randomization, or to use a central randomization institute (particularly in case of a multicentre trial), or a Web-based randomization service. The crux is to conceal the randomization schedule to prevent manipulation of allocation to the different treatment arms. It is preferable to randomize as shortly before the intervention as possible. This prevents dropouts after randomization, for example, when a surgical treatment is inadvertently cancelled.

**Blinding patients and caregivers**

Blinding of patients and caregivers regarding the allocated treatment is recommended. This is the Achilles’ heel of most RCTs in wound care. Whenever possible, the test agents should be masked. This has been successfully performed when testing the effects of zinc oxide \(^{21}\) and ibuprofen \(^{22}\). Blinding is obviously impossible when comparing, for example, negative pressure wound therapy (NPWT) with conventional wound dressing materials. This may introduce performance bias, i.e., patients and caregivers may act differently if they are aware of the treatment given (e.g., patients in the control group may be more likely to use additional care, and patients who know they are in the intervention group may experience placebo effects). Unequally applied co-interventions generally diminish the contrast between the treatment effects, for example, when the amount of antibiotics or analgesics given or the frequency of visits or follow-up intervals differs between the groups. Therefore, these should also be recorded. Some wounds may require a number of unavoidable procedural interventions to promote healing, e.g., regular episodes of debridement. This is acceptable when applied and recorded commensurately in both treatment groups.
Blinding outcome assessors

An independent outcome assessor who is unaware of the treatment given can conquer the challenge of blinding in wound care. It can be helpful to give patients instructions not to tell the independent outcome assessor to which intervention they were allocated. This is particularly relevant in studies in which it is difficult for patients not to discuss the intervention, for instance, when their wounds are treated with NPWT or debrided with maggots.

Blinding of the outcome assessors is important, particularly in wound care, because most of the outcomes (see the section “Study outcomes”) are subjective and open to overestimation in favour of the new intervention (e.g., wound healing). Only if the outcome parameters are objective, such as death, does this become less imperative. Some outcomes are difficult to measure objectively (e.g., patient comfort), while others (e.g., pain) can prove time-consuming and/or expensive.

Intention-to-treat principle

In wound care, some patients may switch from one intervention to the other due to side effects, apparent lack of effect, lack of treatment compliance, or simply a change in preferences. Despite these switches, one should analyse every patient in the group to which they were originally allocated, even if they did not receive the treatment as defined by the protocol or they withdrew from the study. The reason for this intention-to-treat principle is that it maintains treatment groups that are similar (apart from random variation). It therefore validates the use of randomization, and allows for handling of protocol deviations, further protecting the randomization process. If some patients would have been excluded who did not complete their treatment because it was too burdensome (e.g., the use of sheepskin as they developed skin irritation) or because they responded poorly, only the responders will contribute to the—obviously overestimated—treatment effect. Comparing the treatments the patients actually receive (also known as “per protocol” analysis), rather than to which they are allocated (e.g., after crossing over to the other treatment group), confounds the initially equal distribution of patients at randomization.

Main clinical issues

Comparability of study treatments

The comparator treatment should be current best practice rather than placebo. Particularly in acute wound care, there may be little consensus about what constitutes
standard policy, making the comparator choice difficult. Another consideration regarding the interventions in the trial groups is their uniform application. Factors such as dressing change frequency, leg elevation, adequate compression, pressure relief, moment of applying an antiseptic or drainage device, cleansing procedure, antibiotics, and treatment duration are important procedures to standardize. Those who will perform the intervention or apply the device, dressing, or topical agent will benefit from training and instructions on how to use the intervention before the start of the trial. It is also essential to define the indication for, and use of, additional treatments ("co-interventions") such as wound bed preparation, debridement, pain management, additional medication, nutritional supplements, antiseptics or antibiotics, and surgical procedures to avoid differential application. If the latter occurs, the groups are not treated equally and the effect found cannot be attributed only to the intervention under investigation. This flaws the validity of the trial.

Study outcomes

One should choose primary and secondary outcomes carefully and beforehand, as well as how, through which (valid) methods, and after which time interval(s) these outcomes will be assessed.

Primary outcome(s)

This outcome should represent the main effect of the intervention and is used for the sample size calculation (see section Predefined Plan for Data Analysis). The clinical effect of any intervention should be based on outcomes that are meaningful to patients. One may choose a valid intermediate or surrogate outcome if complete wound healing is not the primary aim (e.g., suitability for secondary surgical closure in the case of vacuum assisted closure [VAC] treatment). Then, goals shift toward maintaining or enhancing functional status, optimizing wound condition, or relieving suffering, for example, pain relief in patients with chronic leg ulcers. One should not settle for such end points just to shorten the follow-up period. For example, a 50% reduction in bacterial count might seem an impressive result to the researcher, but the patient still suffers from having a colonized wound. The follow-up should be long enough to measure all predefined outcomes. By definition, chronic wounds are due to an underlying aetiology (e.g., venous hypertension in venous leg ulceration). Consequently, if the aetiology is not resolved, the risk of the lesion recurring over time has to be considered. This eventuality demands months or years of follow-up. Similarly, a study on quality of healing (e.g., hypertrophy, keloid) would also require an extended follow-up period. Moreover, many patients with chronic ulcers are subjected to polypharmacy, thus increasing the risk of drug-associated delays of wound healing. Unfortunately, sometimes less clinically relevant endpoints substitute primary outcomes when the latter were not as good as expected.
Secondary outcomes

In a study regarding preferences on ideal wound dressing characteristics, a short wound healing time, minimal pain during dressing changes, and short duration of hospital stay were valued most.\textsuperscript{26} Meticulous wound pain assessment, preferably using standardized Visual Analogue Scale, and proper documentation of pain and analgesics usage is essential to appreciate an important aspect of wound care.\textsuperscript{27} In addition, any complications or adverse effects should be recorded, such as toxic or allergic responses to dressing materials, blistering, infection, malodour, leakage, unexpected need for redressing, or wound recurrence. If there is a non-negligible risk of serious adverse effects, a data safety monitoring board is required to monitor these events. Adverse effects are usually underreported in publications, but are important to be aware of to weigh the benefits against the possible harms of an intervention. Examples of this are the underestimated adverse effects of silver sulfadiazine for burns and the overestimated ones of iodine as antiseptic agent.\textsuperscript{28-30}

It is of value to also consider assessing quality of life, functional status, and patient satisfaction because it provides valuable information on the patient-perceived burden of illness.\textsuperscript{31} Both generic questionnaires, e.g., the Medical Outcomes Study Short Form-36\textsuperscript{32} or Nottingham Health Profile\textsuperscript{33}, and wound type specific questionnaires\textsuperscript{34} may be combined. In chronic wounds, these measurements should be repeated after larger intervals to determine the long-term effects of the interventions.\textsuperscript{35} For the purpose of comparability among studies, uniform time points for clinical follow-up are highly desirable. Furthermore, the cosmetic result after complete wound healing is an outcome often appreciated by patients.\textsuperscript{36}

In today's economically constrained health services, the costs of treatment are an indispensable outcome parameter.\textsuperscript{37} Therefore, one should try to measure cost-effectiveness from a societal perspective, including all relevant medical costs and nonmedical costs.\textsuperscript{38} Analysis of medical costs should include the unit costs of all (dressing) materials used, costs of personnel involved in wound care, and inpatient treatment period required; costs of immediate and long-term complications; and costs of long-term outpatient monitoring and care. Additionally, the nonmedical costs may be calculated based on costs due to incapacity for work, transportation to the hospital, home adjustments, cleaning of soiled clothing, and so on.

The Cochrane Wounds Group also strongly advocates using only valid, objective outcomes. The proportion of wounds completely healed at a particular time, rates of healing, and incidence of new wounds or infection are considered suitable as primary outcomes.\textsuperscript{39} The FDA guidance formulated definitions of outcomes that can be used to
measure efficacy in wound care research. It helps to define outcomes for chronic and burn wounds, as well as for acute wounds.40

Finally, it is mandatory to store the study database securely and ensure it is available for audit and access. Furthermore, these data may be also valuable for future meta-analysis.

**Predefined plan for data analysis**

A comprehensive study protocol includes a predefined plan for statistical data analysis, which underpins the formulated hypothesis and helps to answer the research question. A meaningful comparison between treatment groups is possible only if an RCT is adequately powered to detect a predefined, clinically relevant difference in the primary outcome, should such a difference exist. For this purpose, one can make a calculation of the required number of patients to be included before the start of the trial. A power (1 – b) of at least 0.80 is considered acceptable, which indicates that there is a 20% risk that a true difference in treatment effect remains undetected, should such a difference exist. In addition, a significance level (a) of usually 0.05 is considered appropriate, meaning that it is accepted that there remains a 5% risk that a difference found is not a true treatment effect, but merely based on chance. We strongly recommend consulting a biostatistician or clinical epidemiologist for the study design and statistical analysis before designing the protocol.

When analysing the data, remember to use the intention-to-treat principle for the reasons explained above. Subgroup analysis may also be considered to examine the treatment effect in a specific group of patients or wounds in the trial, in which the treatment is expected to be more effective. It is important to define such analysis before starting the RCT to avoid the suspicion of “data dredging.” Moreover, such a comparison with less than the initial, complete set of patients is always underpowered and any differences found may be coincidental.

**Discussion**

The scale of the worldwide wound care problem seems to match the high volume of publications, with at least 150,000 hits in Medline related to wound care. These PubMed-indexed studies include opinion-based reports, epidemiological studies, and studies of diagnosis, prognosis, and therapy. A strikingly small proportion of the publications on therapeutic interventions are comparative or randomized studies, and even fewer are (Cochrane) systematic reviews. Most of these Cochrane reviews end by concluding that
the volume and quality of the existing research is low, the consistency of study design is lacking regarding study outcomes, few replication studies exist, meta-analysis is mainly impossible due to heterogeneity of the studies, and most studies are at high risk of bias.\textsuperscript{7}

To enhance the depth and validity of newly generated evidence needed to support clinical decision-making in wound care, we propose this comprehensive framework for wound care researchers to undertake properly designed and executed RCTs. Timely contemplation of methodological rigor is pivotal to achieve the desired scientific knowledge. Many barriers and issues of RCTs can be overcome by proper design and conduct. Understanding the rationale for this comprehensive framework is also important for policymakers to help with decision-making with regard to the plethora of wound care products and the limited financial resources.

A more consistent approach as to the design and conduct of RCTs will facilitate meta-analysis of original studies. Many researchers and clinicians plead for more consistency in the choice of comparators and outcomes to be measured and reported in future research.\textsuperscript{37,41,42} We hope the recommendations given here will help contribute to uniform, high-level research in this realm. Thus, the framework should ultimately help caregivers in decision-making for their patients with wounds. We do realize that this framework does not address the reporting of a trial, which is another essential aspect besides appropriately designing and conducting a trial.\textsuperscript{43}

The obstacles we face when initiating and performing RCTs in wound care are also shared by other clinical areas such as surgery.\textsuperscript{44,45} Indeed, Farrokhyar et al. identified several factors that influence the internal validity of surgical trials. Nevertheless, many of these challenges can be overcome, and in most cases, these issues do not restrict the conduct of an RCT\textsuperscript{45}. This seems to be in contrast with the European Wound Management Association position document\textsuperscript{37}, which also supports the use of cohort studies in wound care. According to Bell-Syer et al., the use of observational studies for evaluating treatment effects is only recommended in very specific circumstances, such as studying rates of diseases or harmful effects.\textsuperscript{7}

Another reason for the seemingly reluctant attitude toward rigorous trials may be the fact that commercially available wound care products, such as dressings and topical agents, do not (yet) need to undergo the scrutiny that pharmaceuticals do before being marketed because they are not subjected to the same rigor by FDA or good clinical practice regulations. Therefore, this does not force manufacturers to perform extensive research on their products. Nevertheless, evidence-based practice has become necessary in an area where clinicians increasingly have to justify their decisions toward patients, insurance companies, and government, and liability issues have become too common.
Given the worldwide magnitude of the wounds problem, health care professionals as well as manufacturers of wound care products should take every effort to improve the quality of care for patients with wounds. The recommended standards presented here for optimum trial design in wound care research are an earnest attempt toward achieving this goal while recognizing that their implementation is not without its own particular challenges.
References


Fundamentals of randomized clinical trials in wound care: reporting standards

F.E. Bröllmann
A.M. Eskes
B.E. Sumpio
D. Mayer
Z. Moore
M.S. Ågren
M. Hermans
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Wound Repair and Regeneration 2013
Chapter 5

Abstract

In wound care research, available high-level evidence according to the evidence pyramid is rare and threatened by a poor study design and reporting. Without comprehensive and transparent reporting, readers will not be able to assess the strengths and limitations of the research performed. Randomised clinical trials are universally acknowledged as the study design of choice for comparing treatment effects. To give high-level evidence the appreciation it deserves in wound care, we propose a step-by-step reporting standard for comprehensive and transparent reporting of RCTs in wound care. Critical reporting issues (e.g. wound care terminology, blinding, pre-defined outcome measures and a priori sample size calculation) and wound specific barriers (e.g. large diversity of aetiologies and co-morbidities of patients with wounds) that may prevent uniform implementation of reporting standards in wound care research are addressed in this article. The proposed reporting standards can be used as guidance for authors who write their RCT, as well as for peer reviewers of journals. Endorsement and application of these reporting standards may help achieve a higher standard of evidence and allow meta-analysis of reported wound care data. The ultimate goal is to help wound care professionals making better decisions for their patients in clinical practice.
Introduction

In the present era of evidence-based medicine, the use of best available evidence has become an essential part of clinical decision-making to ensure and improve quality of care. The requirements to meet this hunger for evidence are: firstly, a proper design and conduct of studies rendering convincing evidence; and secondly, a clear and concise, but at the same time comprehensive and unbiased description of the conducted research to show the validity of the study and the effect of the intervention investigated.

In wound care research, available high-level evidence according to the evidence pyramid\textsuperscript{1} is rare and threatened by either a poor study design or inconclusive results.\textsuperscript{2-6} Nevertheless, the number of scientific publications in wound care shows a 30-fold increase over the last five decades.\textsuperscript{7} During this period, numerous guidelines and recommendations have been developed to improve the quality of design and conduct of wound care research.\textsuperscript{3,5,8}

Unfortunately, upgrading the quality of a study design does not automatically improve the quality of reporting in wound care publications.\textsuperscript{4,9-11} First, positive study results tend to be published more often than indifferent or negative study results, known as publication bias. Second, adverse events may be neglected or reported selectively (also known as reporting bias, caused by the researchers). Third, the nomenclature of essential terms or presentation of the results may differ from other publications in similar areas.\textsuperscript{6,12-15} These sources of bias emphasize the need for full and transparent reporting of wound care research, which will allow the readers to assess the strengths and limitations of the research performed and may also protect clinicians from integrating biased results in their clinical decision-making.\textsuperscript{12}

Besides improving the quality of a study design, the (updated) Consolidated Standards of Reporting Trials (CONSORT) statement has been published with the goal of improving the reporting standards of randomised clinical trials (RCT).\textsuperscript{16} Many scientific journals have endorsed this statement or have incorporated it in their instructions for authors.\textsuperscript{17} Even though these recommendations have had a positive effect on the quality of reporting standards\textsuperscript{18}, huge variation exists in terms of implementation.\textsuperscript{19,20} Wound specific barriers (e.g. variety of aetiologies and multiple factors influencing the wound healing) and the lack of specification in the CONSORT statement for wound care may prevent the uniform implementation of reporting standards in wound care research.\textsuperscript{21}

Despite international recognition of RCTs as the putative ‘gold standard’ for effectiveness\textsuperscript{3,22,23}, this design is relatively seldom used for wound care treatments.\textsuperscript{2-4,24-26}
Specific barriers to perform RCTs in the realm of wound care\textsuperscript{27,28} include the large diversity of aetiologies and co-morbidities, the plethora of treatment options, and invalid or unreliable assessment of outcome measures, which hamper adequate performance and reporting of RCTs. This often leads to the unsatisfying conclusion that ‘there is a need for large, high-quality RCTs in wound care.\textsuperscript{29-31}

To give high-level evidence the appreciation it deserves in wound care, we propose a step-by-step standard for comprehensive and transparent reporting of RCTs in wound care. These recommendations may result in uniformity of publication output; allow meta-analysis of reported wound care data and thus contributing to the potential for improving the quality of wound care delivery.

**Reporting standards**

**Title and abstract**

The title should point out the major aim, result or finding of your study.\textsuperscript{32} The revised CONSORT statement requires identification of the study design in the title.\textsuperscript{16} A carefully chosen title, keywords (if required), and a well-structured abstract helps indexing your publication for easy retrieval as an RCT. At the end of the abstract the trial registration number should be stated as well as the database in which it is registered for reasons given in the Methods section. Common databases include http://www.controlled-trial.com, http://www.icmje.org, http://www.clinicaltrials.gov and http://trialregister.nl.

**Introduction**

The introduction compactly defines the problem (i.e. the area of uncertainty) and its importance in general, what is known about the topic in the literature and identifies what is yet unknown. This illustrates the importance of performing this particular wound care study.\textsuperscript{33,34}

In the first part, summarize, refer and elaborate on the scientific background, related to your research question. A convincing identification of the key issues in current literature is required to set the scene for your trial.\textsuperscript{33,35} In wound care, prevalence numbers of wounds or systematic (meta-) reviews regarding the intervention are often limited. Nevertheless, strive to summarize the best available and up to date evidence or refer to national databases to sketch the size of the wound-related problem, including the overall impact on health and social gain.
Furthermore, state the benefits of study completion. For this article, we state that the gain of reporting standards will be “uniformity of publication output and allowing meta-analysis of reported wound care in the future”. You may want to use “what (will happen) if we have the results”- scenarios to formulate these perspectives.

The last paragraph of the introduction section states the aim of the study, the rationale, the specific objectives and the hypothesis or purpose. For example, “Ageing populations living with chronic wounds”, “variation in wound care”, or “innovative wound materials launched on the market without sufficient evidence for effectiveness”, could motivate the initiative or perspective of the study. The aim of the study should preferably be formulated along the PICO acronym, describing the Patient’s problem, the Intervention under study, the Comparator or standard intervention, and the Outcome parameter(s) of interest.

**Methods**

In general, describe how you performed your RCT in such a way that any research-orientated reader could evaluate and repeat your work.

The Method section is pivotal for the reader to appreciate the validity of a trial and to facilitate the choice for further reading. Assist your reader to interpret the quality of the trial ("did you do the best you could?") and the possible sources of risk of bias ("does the reader believe your results?"), as high-level research methods do not preclude important risks of bias.\(^3\) Wound care research is sensitive to some particular forms of bias, which may have serious impact on the reliability and generalizability of the results. For example, an adequate and concealed randomisation procedure, clear eligibility criteria, \textit{a priori} sample size calculation and the powering of the study, intention-to-treat analysis, blinding of at least the outcome assessor, and duration and completeness of follow-up are regularly under-reported or even overlooked, which may cause justified suspicion of bias.\(^6\)

In wound care, terminology is known to vary among nations, disciplines and caregivers.\(^3\) Therefore, state or describe your definitions clearly, especially when confusing terminology exists, e.g. wound aetiology, regarding debridement, measurement of wound healing or categories of wound dressing materials.

To assist readers in judging your results and any potential sources of bias, report the following criteria, which are essential in wound care.

- Clearly define your inclusion and exclusion criteria, e.g., aetiology of the wound, wound size, internal controls (e.g. whether two wounds are required or a single wound is split in half to test the intervention and control treatment), duration of the wound,
previous treatment received (e.g. debridement and standard treatment), prognostic factors that may impair wound healing (e.g. smoking, diabetes, obesity, weight loss, the use of systemic corticosteroids, radiation therapy). This helps the reader to judge the generalizability of your study results.

- Without a sample size calculation, the reader cannot assess whether observed differences are meaningful and representative for the truth in real life. When no preliminary data exist to determine your sample size, which is often the case with prevalence of (acute) wounds or complications, motivate why a certain anticipated wound occurrence, infection rate, or pain reduction is *clinically* relevant. Small sample sizes in wound care often require the use of restriction (to achieve balance between groups in size or characteristics), as compared to the "simple randomisation" in larger trials. The methods used to restrict the randomisation, along with the method used for random selection, should be specified (such as blocking and block sizes). If stratified randomisation is applied, report why variables are likely or known to influence the outcome in a substantial way (e.g. ulcer duration, wound size or centre).

- In wound care the unit of randomisation might be patients wounds or clusters. Report and explain why either one is chosen as a subject of randomisation. Inclusion of multiple wounds per patient may introduce problems such as interdependency and overestimation of the precision.

- Specify the method of sequence generation, such as a random-number table or a computerised random number generator, providing your reader sufficient information to assess the likelihood of bias in the group assignment.

- Report how the patient allocation is concealed, e.g., by central allocation or by sealed envelopes. This allows the reader to judge whether enrolment of patients can be influenced by foreknowledge of the treatment assignment.

- Report who generated the allocation sequence, who enrolled participants, and who assigned participants to trial groups. Even a perfect randomisation schedule can lead to bias if implemented incorrectly.

- Many wound care products or interventions leave recognizable marks (e.g. negative pressure therapy or tissue adhesives), which makes blinding complicated. Report attempts to solve the blinding issues, e.g. covering the wound material with the same secondary dressings. If blinding is not possible, the importance of using a blinded assessment technique (as objective as possible) becomes vital and should be reported (e.g. wound healing was assessed by an independent caregiver who is blind to the treatment given).

- Define the wound treatment in terms of devices, materials, technology or drugs, brands, dressing change frequencies, dosages and / or sizes of the materials used. If the interventions change during the healing process, also document the condition of the wound or the wound-healing phase at the time of change. Document possible
influence of the caregiver providing the intervention (e.g. expertise, education level, or familiarity with the wound material or device). You may want to describe solutions to prevent expert-based bias by means of protocols (e.g. dressing instructions provided by the manufacturer, or documentation of the wounds with uniformly taken digital photographs). Furthermore, co-interventions should be reported (e.g. antiseptics used in case of local infection). Interventions like antibiotics, secondary dressings, or compression therapy can especially influence the outcome of wound healing or infection rate.

- Report how and when your outcome measures were assessed and why they are considered as patient relevant. For example (time to) complete healing seems to be more relevant to patients than a proportion of the wound area healed. This is especially true for acute wounds, whereas for complex wounds the reduction of pain or slough or percentage of healing can also be considered patient relevant.

- The relation of the outcome measure to the intervention needs to be explained and why this is an objective measure (e.g. assessment was blinded by an independent caregiver or researcher with a validated outcome tool). Report these outcome measurements accurately, so that your study results are reproducible and their validity can be judged. Important outcomes in wound care research are wound healing, reoccurrence of wounds, number and proportion of complications / adverse events, quality of life, length of hospital stay, number of visits to the outpatient (wound) clinic, and costs.\(^{38}\)

- State the duration of the follow-up period. This is especially important for the reader to interpret outcomes such as wound healing, infection, scarring or re-occurrence of the wound. Also, authors of systematic reviews can only perform meta-analysis when the follow-up periods are homogenous. Considering meta-analysis report the mean and standard deviation, however when your data are skewed also present the median and interquartile range.

For larger trials, the study design and methodology may be published beforehand in the form of a study protocol, which will improve the standard of wound care research\(^ {39}\) by enabling:

- The publication of a comprehensive study protocol with relevant details as in the final publication of the results of the study space is limited and it is often not possible to report all kind of details;

- Researchers to obtain feedback on their study design through peer review;

- Readers to compare what was originally intended with what was actually done (thus preventing ‘data dredging’ and post-hoc revisions of study aims);

- Funders and researchers to see which studies are underway and, hence, reduce duplication of research efforts;

- Authors of systematic reviews to find trials (ongoing or unpublished), which may in turn reduce distortion of the evidence due to publication bias.
As an author you may refer to the published study protocol for further details on the protocol. Regardless of whether a protocol has been published, it is important to provide the fundamental elements of the CONSORT checklist in your manuscript to show that the conduct of the trial has been performed according to good clinical practice rules.\textsuperscript{3,16,40}

Clinical trials should be registered in an international trial (meta-) register before they start. State the registration number in your manuscript\textsuperscript{41}, and preferably also in the abstract. Formal approval by the institutional review board or similar ethics board should be stated, or whether the study was deemed exempt from formal approval, e.g., when subjects were studied anonymously without any intervention that might compromise their physical or psychological integrity. Furthermore, all ethical issues should be reported in order to demonstrate good clinical practice and ensure patient safety.

When discussing statistics, your reader should be able to judge the validity of the findings. Only use statistics as relevant to the data you have gathered, with respect to the underlying assumptions governing the use of the specific statistical test. Statistics should be used to scientifically corroborate your conclusion rather than to “chase” a statistically significant result. Avoid the use of statistics solely to impress your reader, as most readers will be deterred by elaborate or complicated statistical methods. Always report in advance planned (subgroup) analyses in your method section to avoid post-hoc analyses that may have the appearance of data dredging. Explain why certain calculations were made to analyse your data. In case of stratified randomisation, an adjusted time to event analysis needs to be reported to correct for the stratification. The data and/or statistical analyses are usually presented in the last subsection, as it leads the reader to the Results section.\textsuperscript{33}

Results

In general, check for internal consistency of data and results within your manuscript, as minor differences in the data presented may be viewed unfavourably by the reviewers and editors.\textsuperscript{42}

A flow chart or diagram of study participants through each stage is recommended.\textsuperscript{16} This is vital for patients with difficult to heal wounds, who are more likely to be lost during follow-up and thereby increase the risk of attrition bias. Report patient exclusion, protocol violations, losses to follow up, cross-over patients and drop-outs for each group and the reasons for these occurrences (e.g. painful dressing changes, leakage, allergic reactions to materials, (serious) adverse events, poor compliance, logistical reasons, moved or deceased patients). As incomplete outcome data may result in bias, report the overall proportion of participants with missing outcome data, reasons for missing
outcome data, difference in proportion of participants with missing outcome data and address the problem of this in your analysis.

State whether you performed an intention-to-treat analysis, and whether or not the patients received or completed the wound care treatment they were allocated to. This helps the reader to judge whether those not adhering to the protocol may have inferior outcomes.

Furthermore, precisely report the eventual duration of the follow-up period. For example, report range of follow-up duration, mean follow-up period with standard deviations and if your data are skewed also report median values with interquartile ranges. Avoid empty terms like “until sutures were removed” or “until complete wound healing”, without providing the actual figures.

Given the diversity of wounds, provide the reader with a detailed and full description of your population and setting at baseline including the eligibility criteria mentioned in your method section. Important demographic characters in particularly complex wound care research are; age, sex, ethnics, type of wound (in relation to aetiology), duration of existence of the wound, size and depth of wound, concurrent illnesses. Medications and relevant prognostic characteristics may influence wound healing or adverse events. These demographic and prognostic factors are usually summarised for each trial arm in the first table. Here, p-values should be avoided because any baseline differences between the randomisation groups, if the randomisation is applied correctly, are due to chance. The p-value represents this possibility of differences being due to chance and are therefore by definition a p-value of 1.0.

Provide absolute numbers when feasible, in addition to percentages (i.e. 30/60 (50%)) and averages (e.g. mean or median) with their variability (standard deviation or inter-quartile range). Means and standard deviations are preferred in order to perform future meta-analysis. However, they are sensitive to outliers and in case of skewed data a median with accompanying interquartile range should also be reported. If patient imbalances occur, report the post-hoc subgroup analysis for each outcome separately.

Always report pre-defined outcomes, benefits and harms as mentioned in the method section to prevent selective reporting. When presenting the results, illustrate the size of the treatment effect (effect size) and the estimate of this treatment effect (point estimate or precision). Effect size should be presented in terms of relative risks (RR), risk difference (RD) (also known as absolute risk reduction (ARR) / increase (ARI)), number needed to treat (NNT) or number needed to harm (NNH) with their precision expressed as 95%
confidence intervals (CI). This modern presentation of study results helps your readers understand the clinical relevance behind the statistical significance.

When reporting time-dependent parameters (e.g. time to wound healing) remember that these events should be analysed by means of survival methods (time to event) and log-rank tests rather than by presenting averages (e.g. average time to wound healing). Mean healing time is solely justified if all patients stayed in and healed during the study period. To report on wound-related harms such as pain, infection, and scar formation, use the time of measurement, the scale of the tool used for assessing the adverse events (e.g. validated pain assessment scale (Numeric Rating Scale or Visual Analogue Scale) or scar assessment scale (e.g. Patient Observer Scar Assessment Scale or Vancouver Scar Scale), relevant co-interventions (e.g., antibiotics when assessing infection) and prevalence or background risk of the adverse event (e.g., wound infection usually is such a rare event that the numbers are too low for a meaningful comparison).

Finally, it is important to disclose any financial subvention, whether this is an unrestricted grant or sponsored. This may reflect the degree of involvement of the sponsor in the interpretation and presentation of the trial results.

**Discussion**

The main purpose of this section is to answer your research question and help readers to understand its consequences in terms of its implication for practice, policy, education or future research.

Do not repeat all your results; instead, start the discussion with your factual results, its interpretation and what these mean for clinical practice and clinical decision-making. The section provides an opportunity to give theoretical explanations, to compare your results to other, similar research, to extrapolate to other wound types, or to discuss any weaknesses in your methods or results, and to provide suggestions for future research.

Wound care research often has to deal with limitations, such as open studies (no blinding), small sample sizes (power), subjective outcome measures (e.g. leakage of wounds), presence of co-morbidities (e.g. diabetes influencing the outcomes wound infection or wound healing), short follow-up periods and industry sponsorship. For example, report the possible influence of lack of blinding on the outcome measurement.

All too often, a positive message of effectiveness is conveyed, whereas the benefits and relevance to patients of the intervention should be weighed against its possible harms, adverse effects and costs. Also, while pragmatic wound care studies may provide more
useful information for routine clinical interpretation (external validity or applicability), they also introduce the possibility of bias (e.g. local differences in treatment of patients, assessment or treatment given is influenced by different wound care providers with different levels of knowledge or experience regarding the wound material).

Depending on the journal style, you may conclude with perceived study results and their possible implications for practice at the end of your discussion or in a new sub-heading ‘Conclusions’. When writing your conclusions make sure they are coherent to your study results and your discussion.

**Final considerations**

In general, the first preparatory step of the writing process is to contemplate the scope and requirements of a suitable journal to entrust your manuscript to. The multidisciplinary character of wound care should influence your decision about your intended readership (e.g. doctors, nurses, educators, or managers of wound clinics) before choosing an appropriate journal.

Broad endorsement of reporting standards is needed to improve the quality of evidence-based wound care. Explanation and elaboration of uniform reporting standards specific to wound care will help the clinical readers, reviewers and journal editors to interpret and critically appraise the wound care literature. Furthermore, it helps to overcome the ambiguity between quality of reporting and the quality of the underlying research (i.e. flaws in study design vs. poor reporting).

Regardless of the on-going debate regarding whether RCTs in wound care are uniquely difficult, wound care continues to be a substantial problem and the need for adequate design, conduct, and reporting of scientific research remains standing.\(^{25,27,43,44}\) Any (potential) flaws in the design and conduct of RCTs in wound care should at least be appropriately addressed and reported in detail in order to reduce confusion regarding the inference of the research.

Table 1 summarizes some critical reporting issues based on the step-by-step reporting standard for RCTs in wound care as described here. This can be used as guidance for authors who write their RCT as well as for reviewers of journals. Endorsement and application of these reporting standards may help to achieve a high standard of evidence, with the ultimate goal to help wound care professionals make better decisions for their patients in clinical practice.
## Table 1. Summary of important reporting criteria

<table>
<thead>
<tr>
<th>Manuscript section</th>
<th>Issue to be described</th>
<th>Clarification</th>
<th>Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>PICO</td>
<td>The aim of the study should preferably describe the Patient’s problem, the Intervention under study, the Comparator or standard intervention, and the Outcome parameter(s) of interest.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wound care terminology</td>
<td>State or describe your definitions clearly, especially when confusing terminology exists, e.g. regarding debridement, type of wound, measurement of wound healing, or categories of wound dressing materials.</td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td>Clear eligibility criteria</td>
<td>Define your inclusion and exclusion criteria to help the reader judge the generalizability of the study results.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definition of outcomes</td>
<td>State a clear definition of the patient-relevant outcomes, which are to be measured in a valid and reliable manner. Good examples are complete wound healing and pain scores using validated assessment tools.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adequate and concealed randomisation procedure</td>
<td>Specify the method of sequence generation to provide the reader with sufficient information to assess the likelihood of bias in the group assignment process.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blinding or objective outcome assessment</td>
<td>Blinding is usually difficult in wound care trials. Report any blinding issues and attempts to solve them, e.g., using a blinded outcome assessor.</td>
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<tr>
<td></td>
<td>A priori sample size calculation</td>
<td>Without a sample size calculation the reader cannot assess whether observed differences are meaningful. Therefore, motivate why your study sample is large enough to detect a clinically relevant difference.</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>Intention to treat analysis</td>
<td>State whether or not the patients received or completed the wound care treatment they were allocated to. This helps the reader judge whether those not adhering to the protocol may have worse outcomes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up duration</td>
<td>Define the exact duration of the follow-up period. Avoid empty terms like “until sutures were removed” or “until complete wound healing”.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Demographic characteristics of the participants</td>
<td>Provide a detailed description of your population at baseline, including wound characteristics and eligibility criteria, to illustrate which spectrum of patients are investigated</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td>Report on all pre-defined outcomes, benefits and harms, as stated in the methods section to prevent selective reporting. Describe the effect size, expressed as relative risk (RR), risk difference (RD), number needed to treat (NNT) or number needed to harm (NNH) with its precision expressed as 95% confidence intervals. Time dependent parameters (e.g. time to wound healing) should be analysed by means of survival methods (time to event) rather than by means of averages (e.g. mean time to wound healing).</td>
<td></td>
</tr>
<tr>
<td>Discussion</td>
<td>Limitations</td>
<td>Discuss study design issues, like no blinding, small sample size, subjective outcome measures, or specific patient groups investigated (e.g. diabetics), short follow-up period, and industry sponsorship.</td>
<td></td>
</tr>
</tbody>
</table>
References


Randomized clinical trial of donor-site wound dressings after split-skin grafting

F. E. Bröllmann
A. M. Eskes
J. C. Goslings
F. B. Niessen
R. de Bree
A. C. Vahl
E. G. Pierik
H. Vermeulen
D. T. Ubbink
on behalf of the REMBRANDT study group

British Journal of Surgery 2012
Chapter 6

Abstract

Background

The aim was to study which dressing material was best for healing donor-site wounds (DSWs) after split-skin grafting as there is wide variation in existing methods, ranging from classical gauze dressings to modern silicone dressings.

Methods

This 14-centre, six-armed randomized clinical trial (stratified by centre) compared six wound dressing materials in adult patients with DSWs larger than 10 cm\(^2\). Primary outcomes were time to complete re-epithelialization and pain scores measured on a Visual Analogue Scale (VAS) over 4 weeks. Secondary outcomes included itching (VAS, over 4 weeks), adverse events and scarring after 12 weeks rated using the Patient and Observer Scar Assessment Scale (POSAS).

Results

Between October 2009 and December 2011, 289 patients were randomized (of whom 288 were analysed) to either alginate (45), film (49), gauze (50), hydrocolloid (49), hydrofibre (47) or silicone (48) dressings. Time to complete re-epithelialization using hydrocolloid dressings was 7 days shorter than when any other dressing was used (median 16 versus 23 days; \(P < 0.001\)). Overall pain scores were low, and slightly lower with use of film dressings (\(P = 0.038\)). The infection rate among patients treated with gauze was twice as high as in those who had other dressings (18 versus 7.6 per cent; relative risk 2.38, 95 per cent confidence interval 1.14 to 4.99). Patients who had a film dressing were least satisfied with overall scar quality.

Conclusion

This trial showed that use of hydrocolloid dressings led to the speediest healing of DSWs. Gauze dressing should be discontinued as they caused more infections. Registration number: NTR1849 (http://www.trialregister.nl).
Introduction

Split-skin grafting is frequently used by surgeons to close skin defects following trauma, ulcers or deep burns.\textsuperscript{1,2} The split-skin harvest technique involves excision of the epidermis and part of the dermis, leaving a donor-site wound (DSW). Although such wounds are created under controlled, sterile conditions, they can be a considerable burden to patients during and after the healing process. They cause itching, pain, infection and cosmetic inconvenience.\textsuperscript{3–5}

Local treatment of DSWs should aim to create an environment that allows rapid and uneventful re-epithelialization, with a minimum of pain, discomfort and hospital stay.\textsuperscript{3,6,7} Based on available evidence, several dressings are suitable for this purpose, ranging from classical gauzes to modern silicone dressings, alginates, films and hydrofibers.\textsuperscript{8–11} However, treatment regimens vary considerably among centres and surgical specialists.\textsuperscript{5,6,8–13}

Available aggregate evidence comprises four systematic reviews based mainly on small trials, from which it is hard to determine the optimal local treatment for DSWs.\textsuperscript{1,6,7,14} Films and hydrocolloids seem most effective in terms of pain relief and patient comfort.\textsuperscript{1,6,15} All the systematic reviews concluded that more convincing evidence is needed.

Apart from the promising evidence regarding hydrocolloids, national surveys have reported on the preferred use in clinical practice of alginates, films, hydrofibres, silicone dressings and gauzes.\textsuperscript{8–11} Hence, these six dressing types were chosen for the comparison in the present trial. This study was conducted to determine which dressing material was best for DSWs after split-skin grafting, in terms of wound healing, pain, complications, itching, costs and scarring.

Methods

A stratified, parallel-group, multicentre randomized clinical trial was designed to compare alginates, films, gauzes, hydrocolloids, hydrofibres and silicone dressings in patients undergoing split-skin grafting (the Recognizing Effective Materials By Randomizing and Assessing New Donorsite Treatments (REMBRANDT) trial). This trial was stratified by centre, with a balanced allocation ratio for each treatment arm using a biased coin\textsuperscript{16}, and was registered as NTR1849 (http://www.trialregister.nl). The
14 recruiting centres included Dutch university hospitals and general hospitals, as well as one of the national burn centres.

The institutional review board of each contributing centre approved the study protocol, which has been published in detail elsewhere. Contrary to this protocol, the group ‘paraffin gauzes’ was renamed ‘gauzes’, because Adaptic® (Systagenix, Gatwick, UK) was used in all but three patients (in whom Jelonet® (Smith and Nephew Healthcare, Hull, UK) was applied). Furthermore, the present methods section highlights only the most important issues according to the revised Consolidated Standards of Reporting Trials (CONSORT) statement.

Participants and data collection

Eligible patients (aged 18 years or older) had a single DSW after split-skin harvest for any indication with a surface area larger than 10 cm$^2$. In patients with multiple DSWs, the allocated dressing was used on all wounds, but a single wound was chosen as the target site. Patients having treatment known to impair wound healing (such as chemotherapy, corticosteroids or local irradiation) and those who could not provide written informed consent were excluded.

Contributing centres provided baseline and peri-operative characteristics, and outcome data for all included patients through the trial website. One trial coordinator stored the data, which were checked for correctness independently by another coordinator.

Dressing materials and nursing time involved in caring for the DSWs were recorded on case record forms by each contributing centre. Patients also noted materials and nursing time in patient diaries during follow-up to facilitate precise registration of these data, particularly in the outpatient setting. Despite repeated efforts, a large number of data were still missing. Given these unreliable data, it was decided not to report on the cost outcome.

Treatment and interventions

The methods of harvesting, local haemostasis and desired thickness of the graft were at the surgeons’ discretion. After skin harvest and haemostasis, the patient was randomized. Randomization was done by an appointed officer in each contributing centre who was not responsible for patient recruitment, or by contacting the trial coordinators. A computer programme (ALEA version 2.2; NKI-AVL, Amsterdam, The Netherlands), hosted by an independent clinical research unit, was used to generate the random allocation sequence for the following dressing groups: an alginate (Kaltostat®, ConvaTec, Skillman, New Jersey, USA; Algisite®, Smith and Nephew; or Melgisorb®, Mölnlycke Health Care,
Gothenburg, Sweden); a semipermeable film (Tegaderm®, 3M, St Paul, Minnesota, USA; or Opsite®, Smith and Nephew); a gauze dressing (Adaptic® or Jelonet®); a hydrocolloid (DuoDERM E®; ConvaTec); a hydrofibre (Aquacel®; ConvaTec) and a silicone dressing (Mepitel®; Mölnlycke Health Care).

The brand names indicate the products actually used in this trial. In three dressing groups the centres were allowed to choose from more than one dressing type to accommodate their local practice. Carers applied and changed the allocated dressings according to the instruction protocol provided before the start of the trial by the different manufacturers of the dressings used. The frequency of dressing changes varied from never (alginate and hydrofibre) to weekly (film and hydrocolloid) or every 10 – 14 days (gauze and silicone). During follow-up carers applied the same dressing type until wound healing was complete.

To ensure equal treatment in all groups, only cotton gauzes and bandages were allowed as secondary dressings. When a DSW infection was suspected, carers were allowed to add an iodine-containing product to a fresh primary dressing. In case of a *Pseudomonas* infection, acetic acid was applied. Additional cleansing or protection during dressing changes was allowed in all treatment groups.

Blinding of patients and care providers was obviously not possible. However, to avoid performance bias, patients were instructed only about how to use their wound dressing and wound care, without expressing any expectations regarding the effectiveness of the dressings in the trial.

**Outcomes**

Primary endpoints were: time to complete wound healing (defined as full re-epithelialization of the donor site without any remaining scabs) and pain measured on a 10-cm Visual Analogue Scale (VAS). Complete wound healing was planned to be assessed by an independent investigator who was not aware of the treatment given. However, for practical reasons, occasionally patients or carers were asked to assess wound healing themselves, which was found to be reliable. Additionally, patients were asked to write down the day of complete wound healing in their personal diary as an additional check. All patients were followed until 12 weeks after complete wound healing.

Secondary outcomes included: adverse events (clinical signs of DSW infection, hypergranulation or allergic reactions), itching (10-cm VAS), and scarring, assessed 12 weeks after complete healing of the DSW by the carers (observers) and patients, using the Patient and Observer Scar Assessment Scale (POSAS). The range of scar assessment
scores varies between 6, indicating normal skin, and 60, indicating the worst possible result. Pain and itching were assessed and recorded in diaries by the patients once a day, approximately at noon, during the first 2 weeks of follow-up and twice a week thereafter for a total of 4 weeks.

**Statistical analysis**

With a 5 per cent significance level and a power of 90 per cent, a sample size of 43 patients per group, that is a minimum total of 258 patients if no dropouts occurred, was needed to detect either a 25 per cent quicker wound healing time or a two-point difference on a ten-point VAS in one dressing group compared with the other five groups combined.

The intention-to-treat principle was applied. To analyse differences in wound healing time and possible effects of the stratification factors on time to an event, the Kaplan – Meier method and Mantel – Cox log rank test were employed. The χ² test was used to examine differences in number of local adverse events, and a general linear mixed model to analyse the differences in pain and itching over time. This model assumes a continuous outcome variable (VAS), which is linearly related to a set of explanatory variables (dressing material used). After the residuals had been checked for normality and model fitting performed, the auto-regressive of order one (AR-1) model was applied. The AR-1 model is one of a group of linear prediction formulas; it allows the co-variable structure for the random-effects model to be specified. For dichotomous outcome parameters the risk ratio (RR) was calculated with 95 per cent confidence interval (c.i.) and number needed to treat or number needed to harm (NNH). Differences in scar assessment scores were analysed using the Mann – Whitney U test as they were non-normally distributed. In addition to the protocol, a Bonferroni correction for both primary endpoints (wound healing and pain) resulted in an adjusted P value for significance of 0.025. SPSS® software (PASW statistics version 18.0; IBM, Armonk, New York, USA) was used for coding and analysis.

**Results**

From October 2009 to December 2011, 358 patients were screened for inclusion, of whom 289 were eligible to be randomized (Fig.1). Baseline demographic and perioperative characteristics were similar among the dressing groups (Table 1), except for the use of haemostasis, which was applied in fewer patients (20 per cent) in the film dressing group. The majority of skin grafts (57.4 per cent) were used to treat a surgical or traumatic wound and were mostly taken from the thigh (270, 93.4 per cent), with a mean (standard deviation (s.d.)) of 0.32(0.15) mm and grafted area of 78.4(109.2) cm². Participating
centres mainly used Kaltostat® in the alginate group and Adaptic® in the gauze group, whereas Tegaderm® and Opsite® were applied equally often in the semipermeable film group.

**Participant flow**

Follow-up was completed in April 2012. During the trial ten patients dropped out; thus follow-up was complete for 279 patients (96.5 per cent). Crossover to another dressing group occurred in 37 (12.8 per cent) of the 289 patients. Crossover varied from three times in the hydrocolloid group to ten times in the hydrofibre group, owing to unfamiliarity with the product (14), preference of the patient (12), infection (6), leakage (3) or logistical reasons (2) (Table 2). The effects of these dropouts and crossovers were avoided by means of the intention-to- treat analysis. The response rate of the patient diaries returned was over 75 per cent, equally divided between the six groups.

**Primary outcomes: complete wound healing and pain**

Time to complete re-epithelialization was 7 days (30 per cent) shorter when hydrocolloid dressings were used (median 16 days) than with any other dressing (median 23 days) ($P < 0.001$) (Fig. 2). Wound healing remained significantly quicker with, or without the
Table 1 Baseline patient characteristics and perioperative data by treatment allocation group

<table>
<thead>
<tr>
<th>Dressing type</th>
<th>Alginate (n = 45)</th>
<th>Film (n = 49)</th>
<th>Gauze (n = 50)</th>
<th>Hydrocolloid (n = 49)</th>
<th>Hydrofibre (n = 47)</th>
<th>Silicone (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>60 (18)</td>
<td>61 (18)</td>
<td>62 (18)</td>
<td>61 (17)</td>
<td>60 (16)</td>
<td>62 (17)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (24)</td>
<td>10 (20)</td>
<td>11 (22)</td>
<td>13 (27)</td>
<td>8 (17)</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Smoker</td>
<td>11 (24)</td>
<td>15 (31)</td>
<td>10 (20)</td>
<td>13 (27)</td>
<td>12 (26)</td>
<td>13 (27)</td>
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<td>Weight loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt; 5 per cent in 1 month</td>
<td>6 (13)</td>
<td>7 (14)</td>
<td>5 (10)</td>
<td>2 (4)</td>
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<tr>
<td>&gt; 10 per cent in past 6 months</td>
<td>4 (9)</td>
<td>5 (10)</td>
<td>5 (10)</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 18.5</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>12 (27)</td>
<td>14 (29)</td>
<td>10 (20)</td>
<td>12 (24)</td>
<td>15 (32)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For DSW</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Not for DSW</td>
<td>11 (24)</td>
<td>14 (29)</td>
<td>15 (30)</td>
<td>17 (35)</td>
<td>13 (28)</td>
<td>10 (21)</td>
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<tr>
<td>I</td>
<td>17 (38)</td>
<td>15 (31)</td>
<td>13 (26)</td>
<td>16 (33)</td>
<td>13 (28)</td>
<td>18 (38)</td>
</tr>
<tr>
<td>II</td>
<td>18 (40)</td>
<td>21 (43)</td>
<td>22 (44)</td>
<td>17 (35)</td>
<td>16 (34)</td>
<td>15 (31)</td>
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<tr>
<td>III</td>
<td>10 (22)</td>
<td>13 (27)</td>
<td>14 (28)</td>
<td>14 (29)</td>
<td>16 (34)</td>
<td>12 (25)</td>
</tr>
<tr>
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<td>0 (0)</td>
<td>0</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Indication for SSG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic wound</td>
<td>10 (22)</td>
<td>8 (16)</td>
<td>10 (20)</td>
<td>13 (27)</td>
<td>6 (13)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>Burn wound</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Surgical/traumatic wound</td>
<td>29 (64)</td>
<td>28 (57)</td>
<td>27 (54)</td>
<td>30 (61)</td>
<td>27 (57)</td>
<td>25 (52)</td>
</tr>
<tr>
<td>Tumour excision</td>
<td>5 (11)</td>
<td>10 (20)</td>
<td>8 (16)</td>
<td>4 (8)</td>
<td>10 (21)</td>
<td>9 (19)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
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<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dermatome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand knife and other</td>
<td>27 (60)</td>
<td>30 (61)</td>
<td>20 (40)</td>
<td>25 (51)</td>
<td>28 (60)</td>
<td>28 (58)</td>
</tr>
<tr>
<td>Electric</td>
<td>17 (38)</td>
<td>16 (33)</td>
<td>24 (48)</td>
<td>21 (43)</td>
<td>13 (28)</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Pneumatic</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td>2 (4)</td>
<td>5 (11)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Location of DSW</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigh</td>
<td>44 (98)</td>
<td>44 (90)</td>
<td>46 (92)</td>
<td>47 (96)</td>
<td>44 (94)</td>
<td>45 (94)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>5 (10)</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>DSW surface area (cm²)†</td>
<td>50.0</td>
<td>49.0</td>
<td>50.0</td>
<td>49.0</td>
<td>37.5</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>(10–240)</td>
<td>(10–600)</td>
<td>(10–450)</td>
<td>(10–800)</td>
<td>(10–750)</td>
<td>(10–760)</td>
</tr>
<tr>
<td>Thickness of graft (mm)†</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>(0.1–0.6)</td>
<td>(0.1–0.6)</td>
<td>(0.1–0.8)</td>
<td>(0.1–0.7)</td>
<td>(0.1–0.6)</td>
<td>(0.1–0.7)</td>
</tr>
<tr>
<td>Haemostasis</td>
<td>18 (40)</td>
<td>10 (20)</td>
<td>23 (46)</td>
<td>26 (53)</td>
<td>14 (30)</td>
<td>23 (48)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (range). DSW, donor-site wound; ASA, American Society of Anesthesiologists; SSG, split-skin grafting.
Bonferroni correction ($P < 0.025$). Median and mean times to complete re-epithelialization for each dressing group are shown in Table 3. Healing times with, and without adjustment for stratification during follow-up showed a significant association between quicker wound healing and hydrocolloid dressings: hazard ratio 2.33 (95 per cent c.i. 1.65 to 3.30) and 1.85 (1.35 to 2.53) respectively.

Overall, pain scores (10-cm VAS), as calculated from 3360 recordings, were low (median 0.4, interquartile range (i.q.r.) 0–1.4). However, they were lower in the semipermeable film group than in the other dressing groups combined ($P = 0.038$, type II test of fixed
Chapter 6

Secondary outcomes: adverse events, itching and scarring

The infection rate with gauze dressings was 18 per cent, which was only slightly higher than when films or hydrofibres were used, but substantially higher than with silicones or hydrocolloids. The infection rate with gauze dressings was twice as high as the mean of the infection rates of the other five dressing groups combined (18 versus 7.6 per cent; RR 2.38, 95 per cent c.i. 1.14 to 4.99; NNH = 10; P = 0.022, χ² test) (Table 3). Allergic reactions were never reported and hypergranulation occurred rarely (Table 3).

Itching scores (10-cm VAS) were calculated from 3579 recordings and were lower (median 0.2, i.q.r. 0–0.8) than pain scores. No significant differences were found among the dressing types.

POSAS data were collected from 137 patients from five contributing centres. Results and summary scores are shown in Table 4. Patients who had semipermeable films were significantly less satisfied with their scars (P = 0.018, Mann – Whitney U test), especially...
Regarding the item ‘wound relief’ (P = 0.046, Mann–Whitney U test). There were no differences in scar assessment by the observers among the dressing types.

**Discussion**

This trial compared six commonly used wound dressing materials to cover donor sites after split-skin harvesting. Use of hydrocolloid dressings led to a 7-day shorter healing time than the other materials. The use of gauze tended to result in a higher risk of infection than other dressing types.

This quicker wound healing with hydrocolloid dressings might be explained by differential wound angiogenesis associated with different degrees of occlusion.\textsuperscript{22} Dressings promoting a moist wound environment, such as hydrocolloids, have been shown to improve re-epithelialization, increase collagen synthesis and ultimately improve healing rates.\textsuperscript{1,23–25} The shorter healing time of donor sites using dressings that promote moist wound healing had already been suggested by previous aggregated evidence.\textsuperscript{1,6,7,14}

This trial now offers evidence for the effectiveness of a specific dressing type within this group of materials. Other occlusive or semi-occlusive dressings, such as foam dressings, might have similar healing effects, but these dressings were not included in the present trial based on evidence from previous literature and a national inventory showing lower eligibility.\textsuperscript{8,14} The (moist) wound environment may also be influenced by the types of secondary wound dressing applied. In this trial the protocol prescribed the uniform use

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**Table 4** Patient and observer scar assessment results by treatment allocation group

<table>
<thead>
<tr>
<th>Dressing type</th>
<th>Alginate</th>
<th>Film</th>
<th>Gauze</th>
<th>Hydrocolloid</th>
<th>Hydrofibre</th>
<th>Silicone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>20</td>
<td>22</td>
<td>21</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>POSAS score*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer</td>
<td>11 (8–14)</td>
<td>11 (10–15)</td>
<td>12 (8–14)</td>
<td>10 (8–14)</td>
<td>11 (9–15)</td>
<td>11 (8–13)</td>
</tr>
<tr>
<td>Patient</td>
<td>10 (7–13)</td>
<td>14 (11–15)</td>
<td>11 (8–14)</td>
<td>10 (8–12)</td>
<td>10 (7–15)</td>
<td>11 (9–14)</td>
</tr>
<tr>
<td>Overall scar rating*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observer</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>2 (2–3)</td>
<td>2 (1–3)</td>
<td>2 (2–4)</td>
</tr>
<tr>
<td>Patient</td>
<td>2 (2–5)</td>
<td>4 (1–4)</td>
<td>2 (2–5)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>2.5 (1–4)</td>
</tr>
<tr>
<td>Patient satisfaction with dressing†</td>
<td>7.7 (4–10)</td>
<td>7.5 (1–10)</td>
<td>8.0 (5–10)</td>
<td>7.6 (1–10)</td>
<td>7.3 (4–10)</td>
<td>7.7 (2–10)</td>
</tr>
</tbody>
</table>

Values are *median (interquartile range) and †mean (range). Patient and Observer Scar Assessment Scale (POSAS): for observer and patient a score of 6 indicates normal skin, and 60 indicates the worst possible result. Overall scar rating: for observer and patient a score of 1 indicates normal skin, and 10 indicates the worst possible result. Patient satisfaction with dressing: a score of 1 indicates very dissatisfied and 10 indicates very satisfied.
of gauze-based secondary dressings. Hence, the effects of other secondary dressings (such as semipermeable film) used in clinical practice could not be studied.8

The time to complete healing in the hydrocolloid group exceeded the healing times reported in other studies, which varied from 10 to 12 days.5,12,13,26,27 This is probably due to the strict definition of complete epithelialization, which stated that complete wound healing was not reached until any remaining scabs had fallen off. This is in contrast with a range of definitions from other studies, including epithelial coverage, absence of exudate, scar appearance and proportion of the wound healed.7 Although the definition used here, and consequently the healing time observed, may differ from that in other studies, it was chosen as an objective, valid, uniform, easily assessable and patient-relevant outcome.19

Overall pain scores were low (mean pain scores varied between 0.2 and 3.0). Regardless of any statistically significance difference, this is unlikely to be of clinical relevance.

The high risk of infection in patients treated with gauze dressings was also found for fine mesh gauze dressings with scarlet red, which had a 9.6 per cent infection rate.28 Patients from all dressing groups in the present trial received systemic antibiotics at a similar rate (21 – 35 per cent), mostly prescribed for indications other than the DSW. Despite the relatively high rate of antibiotic prescription, gauze dressings were accompanied by a significantly higher DSW infection rate, which prolonged healing. However, aggregated results of gauze dressings for DSWs and postoperative wounds did not find an increased risk of infection.1,6,7,14,29

Haemostasis was applied in fewer patients in the film and hydrofibre groups than in other dressing groups; however, the surgeon's decision that haemostasis was not needed was not influenced by the dressing, as the allocation was decided by randomization after haemostasis had been achieved. In the gauze, hydrocolloid and silicone groups, haemostasis was applied in about half of the patients, but time to wound healing differed considerably among these groups, indicating that the need for haemostasis did not have a substantial effect on wound healing.30

Some possible limitations of this trial include: variation in thickness of the skin graft, method of harvesting, and the surgeons' preferences regarding haemostasis and treatment of infection. This was intentional, to allow a pragmatic trial that would mimic daily clinical practice. Furthermore, as in many surgical trials, blinded outcome assessment was not always possible because different dressings leave different imprints on the DSW. However, subjective assessment of wound healing has been shown to be a
reliable and valid method for assessment of epithelialization. Furthermore, a strict definition of complete wound healing was used.

The cosmetic appearance of the scars was assessed after 3 months, even though active remodelling and maturation of scars takes at least 12 months. Nevertheless, the POSAS score is a reliable and valid instrument for identifying changes in scar characteristics. As described in the study protocol, differences in scar development related to the dressing materials investigated. The assumption was that differences seen at 3 months would diminish with time, as shown in other studies.

Finally, it was not possible to report accurately on costs, which play a substantial part in the choice of wound treatment. Unit and total costs of hydrocolloid dressings are high. However, investigators frequently report on unit costs but tend to neglect dressing change frequency, nursing times or rapid healing time, and secondary gains such as early mobilization. In this trial it was difficult to record and report the costs of such factors accurately. However, the costs of local wound treatment should be put in perspective. The relatively high costs per dressing unit are at least in part compensated by a low dressing change frequency (once in up to 7 days), which causes little pain. Besides, patient preferences or priority for rapid healing may downplay the costs of a dressing material, for example in patients with extensive burns or severe co-morbidity. In such scenarios hydrocolloid dressings, which do not need changing frequently, seem preferable to achieve more rapid wound healing.

Comprehensive inclusion criteria (all adults requiring a split-skin graft) was one of the strengths of this trial and allowed application to a broad patient population with DSWs. In addition, the results reflect local practice in 14 national centres, which improves the generalizability. Much effort was put into minimizing the risk of bias due to incomplete outcome data, which resulted in a low dropout rate (3.5 per cent).

Use of a hydrocolloid dressing for DSWs reduced healing time by 7 days compared with other commonly used dressing materials. The results of this study should decrease the current diversity in treatment choices for DSWs as treatment options are now more evidence-based. Several practical considerations should be mentioned about the use of hydrocolloid dressings. Before their application, the skin should be clean; fatty disinfectants should be avoided for better adherence. With large wounds, leakage can be a problem owing to interaction of wound exudate with the dressing. A moist interface between the dressing and the wound, however, reduces postoperative discomfort and minimizes tissue damage during dressing changes.
Collaborators

Other members of the REMBRANDT study group who collaborated in this study: S. J. M. Jongen (Martini Hospital, Groningen, The Netherlands); K. E. A. van der Bogt and J. van Vooren (Leiden University Medical Centre, Leiden, The Netherlands); J. F. A. van der Werff (Haaglanden Kliniek/Nederlands Centrum Plastische Chirurgie, The Hague, The Netherlands); A. K. J. Ahmed and J. van de Geijn (Kennemer Gasthuis, Haarlem, The Netherlands); A. H. Schuurman (University Medical Centre Utrecht, Utrecht, The Netherlands); M. Goedhart and A. van Delft (VU University Medical Centre, Amsterdam, The Netherlands); D. Nio, D. Hoek and W. Vermeulen (Sparne Hospital, Hoofddorp, The Netherlands); N. Koedam (Tergooi Hospital, Hilversum, The Netherlands); P. Heres (Waterland Hospital, Purmerend, The Netherlands); L. Levert-Brand and T. de Groot (Langeland Hospital, Zoetermeer, The Netherlands); E. Harink and M. Waindrich (Isala Klinieken, Zwolle, The Netherlands); J. W. T. Verheijden-Melssen (Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands); and K. Groenhuijzen (Gelre Ziekenhuizen, Zutphen, The Netherlands).

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A.M.E. and F.E.B. contributed equally to this work. Members of the REMBRANDT study group express their gratitude to all patients who participated in the study. They thank Professor Koos Zwinderman for his advice regarding the statistical analysis and Dr Miranda Roskam-Mul for her support in randomizing patients with the ALEA web application; and Henny Teeuwissen, Hanny Schram, Dennis de Bie, Margot van Braak and Sjaak Pennekamp for their invaluable contribution to patient recruitment and support throughout the trial. The study was supported by an unrestricted grant from the Dutch Burns Foundation.
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Chapter 6


part II

Scar formation
Are digital photographs reliable to assess donor site scars? An inter-method analysis and validity testing

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Adapted from short communication:
Chapter 7

Abstract

Background

The Observer Scar Assessment Scale (OSAS) is used to judge scars in vivo and on digital photographs. It is questionable whether these different methods influence the results of the scar assessment. The aim of this study was to assess the inter-method reliability, score agreement and validity testing of in vivo and digital photographic assessments of donor site scars.

Methods

Donor site scars of 119 patients were investigated. Three months after complete epithelialization of the donor site the six items of the OSAS were rated in vivo and from digital photographs. Intra-class correlation coefficients (ICC) were calculated to judge inter-method reliability. Score agreement for each item was assessed using Bland & Altman plots. Validity of the digital photographic assessment was tested by comparing the OSAS outcomes of six wound dressings evaluated in a trial using the in vivo judgements as a reference standard.

Results

Reliability was moderate at best for the ‘total observer score’ (ICC 0.47) and ‘pigmentation’ (ICC 0.45). Bland & Altman plots showed wide limits of agreement between the in vivo and photographic assessment for ‘vascu larity’, ‘pigmentation’, ‘overall opinion’ and ‘total observer scale’. The item ‘pigmentation’ as assessed on digital photographs received a lower score than the in vivo assessment (p=0.027, Mann-Whitney U test).

Conclusions

Reliability between digital photographs and in vivo assessment of donor site scars is limited when using the OSAS. Correspondingly, both methods result in different scar judgements of donor site scars. Therefore, in clinical practice, in vivo assessment of donor site scars should remain the policy of choice.
Introduction

Donor site wounds (DSW) after split skin grafting can be a considerable burden to patients, not only during, but also after the healing process.\textsuperscript{1-3} Often patients endure a wide range of problems related to their donor site scar, varying from aberrant colour and itching to overall quality of life issues.\textsuperscript{4-8} Moreover Cubison et al. found that prolonged healing time increases the risk of hypertrophic scarring.\textsuperscript{9} Consequently the interest for scar research, prevention, monitoring and treatment is rising.\textsuperscript{10-14}

For research purposes, scar quality can be assessed in vivo, i.e. real life, or from digital photographs, each with its pros and cons. Conventional outpatient clinics are suitable for monitoring DSWs and donor site scars through in vivo observations. However, these visits may not be worthwhile when its sole purpose is wound inspection and may be time-consuming for both patients and healthcare professionals, and cumbersome for the patient due to the wound that required the transplantation.

As an alternative, digital photography or, in a broader sense, telemedicine have been proposed as a potential (consultation) tool in the management of donor site scars, as they accommodate the visual nature of skin examination.\textsuperscript{15-17} Digital photographs have been successfully used for repeated wound size measurements in (randomised) clinical trial design\textsuperscript{18-20}, and inter-observer studies\textsuperscript{21-22}. The advantages of digital photographs are their high-quality colour images, which can be easily captured and transferred to a computer, analysed, stored, printed or sent by email. This enables communication across the disciplines involved, which is particularly valuable in wound care due to its multidisciplinary nature. Furthermore, these photographs can be stored as part of an electronic patient record and used in a telemedicine system for shared patient management by community nurses, specialised wound nurses and plastic surgeons.

If digital photographs are used for a uniform judgment and management of donor site scars, valid scar assessment tools are needed. The Patient and Observer Scar Assessment Scale (POSAS) is such a validated tool for the judgment of various types of scars, i.e. burn- and linear scars.\textsuperscript{23-24} The POSAS is a subjective, consistent and feasible tool\textsuperscript{23,25}, which can be used reliably even by inexperienced observers\textsuperscript{6}.

However, little is known about the observer agreement of digital photographs versus in vivo observation when monitoring donor site scars.\textsuperscript{17,26} If we decide to rely on photographs in the management of DSWs, we need to know whether these are as reliable and valid as in vivo judgements. From contiguous research on wound assessment it is known that the inter-observer reproducibility of wound measurements made by using
digital photographs can be as accurate as contact tracing. Others emphasize that lack of live assessment fails to evaluate the wound from multiple visual angles and under various lighting conditions. Furthermore, it does not allow palpation of the wound, which makes three-dimensional defects less obvious. In current research the observer scale of the POSAS, also called the Observer Scar Assessment Scale (OSAS) is used for in vivo and digital photographs as well. However, it is questionable whether these different settings influence the results of the scar judgment and eventually treatment policy.

Therefore, the aim of this study was to assess the inter-method reliability and score agreement of in vivo and digital photographic assessments with the OSAS and validity testing of the digital photographic observations for healed DSWs.

Patients and methods

Patients and equipment

For this study we used data from a multicentre randomised clinical trial regarding the treatment of donor site wounds (REMBRANDT trial, registered as NTR1849). In this trial 289 adult patients, who underwent split skin grafting leaving a donor site area of at least 10 cm², were included to evaluate the effectiveness of six different wound dressing materials (alginate, film, gauze, hydrocolloid, hydrofibres or silicone). The REMBRANDT trial and its study protocol have been described in detail previously. All patients gave written informed consent for the REMBRANDT trial and this inter-method analysis. This study was approved by the medical ethics review boards of the contributing centres.

For this study we selected all patients with complete follow-up data regarding their scar evaluation, conducted three months after complete epithelialisation of the DSW. Complete wound healing was defined as re-epithelialisation of the total wound surface without remaining scabs.

Photographs were taken with digital cameras, with a minimal resolution of five megapixels, in the outpatient clinics or during home visits, by a total of eleven medical doctors, specialized wound nurses, surgical nurses, or wound researchers from five centres. The images were stored in JPEG format in the camera and transferred to a personal computer. Those who took the pictures were also the in vivo observers. Two pictures were taken; one with and one without using flashlight.
Observers and scar assessment

The eleven healthcare professionals performed the in vivo scar judgment independently, using the OSAS. Furthermore, they recorded skin type by means of the Fitzpatrick skin classification, a numerical classification for the colour of skin. Their judgments and photographs were then submitted to the study coordinators (FB, AE). Subsequently, one plastic surgeon (AK), with extensive experience with the POSAS to judge donor sites, independently judged the digital photographs of the donor site scars using the observer scale and recorded the skin type.

The observer scale contains six items, including ‘vascularity’, ‘pigmentation’, ‘pliability’, ‘thickness’, ‘relief’ and ‘surface area’. Each item is scored numerically, ranging from one (best possible outcome) to ten (worst possible outcome), and results in a ‘total score’ of the OSAS. In addition, an ‘overall opinion’ on the dissatisfaction with the cosmetic appearance of the scar was given, also on a scale of one to ten, where ten corresponds with the worst imaginable scar.

Data gathering and analysis

Data and data entry were cross-checked by two investigators independently (AE and FB). Basic demographic data of the patients contained age, sex, smoking status, indication for the split-skin grafting, location of the DSW, thickness of the graft, and skin type.

To assess the inter-method reliability of the OSAS scores obtained from digital photographs and in vivo judgments, intra-class correlation coefficients (ICC), including their 95% confidence intervals (CI) were calculated. ICCs of the separate OSAS items, ‘total scores’ and ‘overall opinions’ were calculated using the one-way random single measures model. We interpreted an ICC above 0.8 as ‘very good’, between 0.8 and 0.6 as ‘good’, between 0.6 and 0.4 ‘moderate’, below 0.4 ‘poor’ and negative values mean no reliability at all.

Score agreement was further assessed using the method of Bland & Altman, which plots the score differences between in vivo and photographic judgments against their averages. This plotting technique allows detection of both random and systematic differences across the range of values measured. Bland and Altman suggested the calculation of “limits of agreement” to indicate the absolute magnitude of the deviation scores. When the measurement error is random, 95% of the deviation scores is expected to fall within ± 1.96 standard deviations. As the OSAS scale for each item varies from one to ten, we considered arbitrarily a two-point variation (i.e. 20% of the total scale) as acceptable. Similarly, we considered a maximum of 20% of the total OSAS scale, i.e. an 11-point difference, as an acceptable variation for the total OSAS score, which varies from six to 60.
Chapter 7

After establishing the inter-method reliability, validity testing of the digital photograph assessment was performed by comparing the OSAS results in vivo with the digital photographs using the in vivo observations as a reference standard. We hypothesized that a (very) good reliability between both methods would result in similar effectiveness outcomes of the wound dressing materials used in the REMBRANDT trial. The differences between the OSAS scores were analysed using the Mann-Whitney U test due to their non-normal distribution.

Data analysis was performed using SPSS v. 18 (IBM, Armonk, NY, USA).

Results

Patients

A total of 119 patients with complete follow-up data regarding their scar evaluation was investigated. They had a mean age of 60 years (SD 16.1, range 18-90), 81 (68.6%) of whom were males (Table 1). Patients needed a split-skin grafting mainly for surgical or traumatic wounds (66.4%). The graft had a median thickness of 0.30 millimetres and was harvested usually from the upper thigh. The in vivo and photograph observers classified

| Table 1. Patient and peri-operative characteristics of the 119 patients investigated |
|---------------------------------|------------------|
| Mean age ± SD, years            | 60.0 ± 16.2      |
| Males, n (%)                    | 81 (68.1)        |
| Smokers, n (%)                  | 36 (30.3)        |
| Indication for SSG, n (%)       |                  |
| - Chronic wound                 | 28 (23.5)        |
| - Burn wound                    | 3 (2.5)          |
| - Surgical/traumatic wound      | 79 (66.4)        |
| - Tumour excision               | 7 (5.9)          |
| - Other                         | 2 (1.7)          |
| Location of the DSW, n (%)      |                  |
| - Thigh                         | 115 (96.6)       |
| - Other                         | 4 (3.3)          |
| Median thickness of graft, mm (range) | 0.30 (0.10-0.80) |
| Fitzpatrick skin classification  | In vivo          | Photograph      |
| - I                             | 14 (11.8)        | -               |
| - II                            | 65 (54.6)        | 102 (85.7)      |
| - III                           | 22 (18.5)        | 9 (7.6)         |
| - IV                            | 6 (5.0)          | -               |
| - V                             | 1 (0.8)          | 2 (1.7)         |
| - VI                            | 7 (5.8)          | 6 (5.0)         |

SD, Standard Deviation; SSG, Split Skin Graft; DSW, Donor Site Wound; mm, millimetres.
the majority of the patients as Fitzpatrick skin type II (white skin with blond or red hair; blue, green or hazel eyes). However, the Fitzpatrick skin classification scores showed a wider range when assessed in vivo than using the photographs (Table 1).

Reliability and agreement on OSAS items and overall opinion

Table 2 shows the reliability of judging photographs using the observer scale items, the ‘total OSAS score’ and the ‘overall opinion’ as compared to in vivo judgments. A moderate reliability was observed for the ‘total OSAS score’ (ICC 0.47, 95% CI 0.32-0.60) and ‘pigmentation’ (ICC 0.45, 95% CI 0.29-0.58). Other items scored poorly or, in case of ‘surface area’, there was no reliability at all (i.e., a negative ICC was observed), as shown in Table 2.

Table 2. Inter-method reliability between digital photographs and in vivo assessment of donor site scars, expressed as interclass correlation coefficients for the OSAS items using a one-way random model (single measurements)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>MD</th>
<th>SD</th>
<th>Inter-method reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICC</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Total OSAS score</td>
<td>-1.6</td>
<td>3.7</td>
<td>0.47 (0.32-0.60)</td>
</tr>
<tr>
<td>Vascularity</td>
<td>-0.9</td>
<td>1.7</td>
<td>0.27 (0.09-0.43)</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>-0.6</td>
<td>1.9</td>
<td>0.45 (0.29-0.58)</td>
</tr>
<tr>
<td>Thickness</td>
<td>0.02</td>
<td>1.0</td>
<td>0.26 (0.08-0.42)</td>
</tr>
<tr>
<td>Relief</td>
<td>-0.3</td>
<td>0.9</td>
<td>0.39 (0.23-0.53)</td>
</tr>
<tr>
<td>Pliability</td>
<td>0.1</td>
<td>1.0</td>
<td>0.30 (0.13-0.46)</td>
</tr>
<tr>
<td>Surface area</td>
<td>0.1</td>
<td>0.5</td>
<td>-0.05 (-0.23-0.13)</td>
</tr>
<tr>
<td>Overall opinion</td>
<td>-1.3</td>
<td>1.3</td>
<td>0.33 (0.16-0.50)</td>
</tr>
</tbody>
</table>

MD, mean difference between in vivo and photographic OSAS scores; SD, Standard Deviation; ICC, Intra-class Correlation Coefficient; CI, Confidence Interval; OSAS, Observer Scar Assessment Scale.

Scores of the following items (‘thickness’, ‘relief’, ‘pliability’ and ‘surface area’) showed nearly always a single value for the in vivo assessments, which precluded the production of Bland-Altman plots. The remaining items; ‘total OSAS score’, ‘vascularity’, ‘pigmentation’ and ‘overall opinion’, were analysed using the Bland-Altman technique (Figure 1). Total OSAS scores ranged between six and 23. The in vivo judgments led to a systematically lower OSAS score, which means better scar quality, for most items investigated (‘total OSAS score’, ‘vascularity’, ‘pigmentation’, ‘relief’ and ‘overall opinion’). Also, the differences between the in vivo and photograph judgments of the items ‘vascularity’, ‘pigmentation’ and ‘overall opinion’ were larger than four and, thus, crossed the predefined limits. This is in line with the poor to moderate agreement regarding each of these items. However, for the ‘overall OSAS score’ the differences were within our predefined limits.
Validation of the OSAS based on digital photographs

In vivo scar assessment scores did not show significant differences among the six wound dressing materials compared in the REMBRANDT trial on any OSAS item or total OSAS score. This was in contrast with the photographic scar assessment, which showed that patients who received alginate dressings scored lower on the OSAS item ‘pigmentation’ \( (p=0.027, \text{Mann-Whitney U test}) \) compared to the other treatment arms taken together.

Discussion

The results of this study show that OSAS assessed from photographs are not a valid tool to judge donor site scars, based on the limited reliability and agreement between digital photographs and in vivo assessment using the OSAS for donor site scars. The inter-method reliability was moderate at best on only two of the six items, ‘pigmentation’ and the ‘total OSAS score’. As expected, considering the characteristics of a photograph,
we found hardly any agreement as to ‘thickness’, ‘relief’, ‘pliability’ and ‘surface area’. Overall, the judgment of scars in vivo and on digital photographs appeared to disagree, resulting in a discrepancy in the judgment of scar quality.

To our knowledge the OSAS has not been validated when using digital photographs, yet they are interchangeably used for scar assessment in post-surgical and DSWs.\textsuperscript{29,30} Because in vivo agreement among caregivers has shown to be valid and reliable\textsuperscript{6,24,}, the (P)OSAS is generally accepted as a scar assessment tool in clinical practice and is rationally used as an outcome measure for scar formation research.\textsuperscript{6,24,32,36,37}

Our validation analysis showed that the lack of agreement can lead to a different perception of the clinical outcome and consequently to a different patient satisfaction. If digital photographs were used in the REMBRANDT trial, alginate would have shown better results based on the OSAS score than the in vivo judgments. We assumed that the in vivo judgment, as reference standard, is superior to the judgement of photographs because the OSAS has been validated in vivo. In any case, both methods are not interchangeable and the consequences of differences in judgment could result in different research results and possibly different clinical choices for wound dressing regimes.

Previous studies, using different (standardised) methods of photographic assessment, report contradicting evidence as to the use of digital photographs in wound care. This makes the value of digital photographs debatable, however popular they may be for, for instance, teledermatology.\textsuperscript{38} Aggregated evidence on the merits of tele-dermatology for various skin conditions shows this remote practice has an inferior diagnostic accuracy.\textsuperscript{17} Moreover, limited evidence exists regarding tele-dermatology as to clinical outcomes and management compared to clinical dermatologists.\textsuperscript{17}

Other studies have shown good inter- and intra-observer reliability for the use of digital photographs.\textsuperscript{16,39,40} Only one study compared the wound area of chronic wounds as assessed by digital photographs and by means of contact tracing and found no significant differences.\textsuperscript{27} These contradicting findings may be due to differences in study population, method of assessing images, or study design.

Four out of the six items of the observer scale; i.e. ‘thickness’, ‘relief’, ‘pliability’ and ‘surface area’, had a low reliability because these are fairly difficult to assess from digital photographs, irrespective of the quality of the images. Because these items contribute substantially to the total observer scale judgement, it is remarkable that the observer scale has not been validated for digital photographs in previous studies before its acceptance in the clinical setting.
Some limitations of our study should be mentioned. First, the photographs used for assessing donor site scars were taken with different digital cameras in different settings (e.g. in-hospitals, outpatient clinics, nursing homes, and patients’ homes). Although we believe that today’s modern digital cameras as used in this study warrant auto-focused, high-resolution pictures with low varying quality, it still may have affected observer scale judgement. Also, standardization of the photographic equipment could have reduced the generalizability of our study results.

Secondly, the OSAS scores when judged from the digital photographs were systematically lower than when judged in vivo. This could be due to a lower quality of the digital photographs or to the fact these pictures were judged by a single observer (AK). Whichever reason may be true, the possible risks of this discrepancy as mentioned above remain lurking. The digital photographs were judged by one observer (AK), which could have influenced the reliability of the results. Yet, the proven inter- and intra-observer reliability of the POSAS tool has been the reason to choose for this study design.6

Finally, we used a sample of 119 patients with complete follow-up data regarding their scar evaluation. Previous studies used samples varied from 20 to 80 patients for inter- and intra observer analysis and validity testing.12,30,41,42 In order to achieve more precise results we used a sample of more than 100 patients as advised by the COSMIN group.43 We were able to confirm the precision of our results by means of a post-hoc power analysis. This analysis showed that the 95% CI would range from 0.36 to 0.64 given an expected ICC of 0.50. This seems a relatively small range, as it would not have changed the conclusion of our study that the agreement is ‘moderate’ at best.

Further research with the OSAS should consider the poor inter-method reliability of digital photographs for scar assessment of donor site scars and, consequently, its failing ability to measure what it is supposed to measure. For other types of scars, reliability and validity testing should be performed before relying on digital photographs.

Our findings suggest that digital photographs are no valid substitute for in vivo judgment of donor site scars using the OSAS. Hence, in this case a picture is not worth more than a thousand words. Therefore, in clinical practice, in vivo assessment of donor site scars should remain the policy of choice. Research findings based on digital images may be inconsistent or invalid, and clinically, this could result in different treatment decisions for various scars. Because these conclusions were drawn merely from donor site scars, similar questions remain to be answered for other types of wound.
Digital photographs to assess donor site scars

Acknowledgement

We owe our gratitude to the patients, specialised wound care nurses, and surgical nurses collaborating in the REMBRANDT study for their contribution to the assessment of the donor site scars. Furthermore, we would like to thank the REMBRANDT study group for including the patients in the REMBRANDT trial.
References

Values of patients and caregivers for donor site scars: An inter-observer analysis between patients and caregivers and prediction of cosmetic satisfaction

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H. Vermeulen

Burns 2012
Abstract

Background
The Patient and Observer Scar Assessment Scale (POSAS) is used to judge scars and involves patients and caregivers. Although the opinions of both are integrated, agreement between them is poorly investigated, especially in donor site scars (DSSs). Furthermore, it is unknown which POSAS-items are mostly associated with overall cosmetic satisfaction with the scar.

Methods
We included 106 DSS-patients. Twelve weeks after wound healing, patients and caregivers rated the DSS in vivo using the POSAS, comprising seven items. They were unaware of each other’s judgment. Inter-observer reliability (IOR) was expressed as intra-class correlation coefficients (ICC). Items of the POSAS that best predicted patients’ overall satisfaction were identified using multivariable regression analysis.

Results
Eleven caregivers from different medical centres judged the DSSs. IOR for the POSAS-items was ‘moderate’ at best regarding the item ‘overall opinion’ (ICC 0.44, 95% confidence interval 0.27 to 0.58). IORs regarding other POSAS-items were ‘poor’. Itching and relief best predicted patients’ overall satisfaction (total variance explained, $R^2 = 0.174$). For caregivers, pigmentation and pliability were most predictive ($R^2 = 0.318$).

Conclusion
Patients and caregivers appreciate different aspects of scar characteristics using the POSAS. This calls for shared decision-making, in which patient opinions are incorporated in the treatment choice.
Background

Scars are undesired manifestations of the normal wound healing process. If located in visible areas, scars may have a psychological impact and could affect the patient’s quality of life. Evaluating scars is important to balance pros and cons of wound care options and make well-informed clinical decisions for treatment of wounds and prevention of scars.

To support the judgment of the eventual healing result, many scales are available to classify scars, such as the VSS (Vancouver Scare Scale), POSAS (Patient and Observer Scar Assessment Scale), MAPS (matching assessment of scars and photographs), and the Manchester scar scale. None of these scales really stands out or is generally accepted, though the VSS and POSAS are mostly used in daily practice. The POSAS is unique in that it takes the opinion of the patients into account and consists of two scales: the Patient and Observer Scar Assessment Scale. Patients and observers, i.e. their caregivers, score slightly different items related to the scar characteristics, e.g. colour, thickness, relief, pliability, and more subjective factors, such as pain and itching. In burn scars the POSAS is considered superior to other assessment scales.

Nowadays, incorporating patient’s values and opinions in the decision process is promoted to ensure high-quality patient-centred care. However, caregivers still tend to overlook or misrepresent the patients’ opinion about their scars, which may lead to external decision-making about treatment choices. Hence, clinicians should be aware of the scar characteristics patients value most. Previous research regarding the POSAS in patients with scars outside the realm of DSS, showed a good agreement among caregivers. This scale has already been validated to classify burn- and linear scars, which suggests its usefulness in DSS after split-skin grafting, as these are acutely created and have a linear shape.

However, up to now it is unknown if patients and their caregivers differ in their perspectives regarding the desired result of the donor site scar (DSS). Furthermore, it is unclear which item (e.g. colour, thickness, or pain) or combinations of items best predicts the overall opinion of patients and caregivers about the scar.

Therefore, the aim of this study was to investigate the extent to which patients and their caregivers agree in their appreciation of the scar using the POSAS and which scar characteristics contribute most to their judgments.
Chapter 8

Methods

Patients

For this study we used data from the patients who were included in our recently completed randomized clinical trial regarding donor site treatment (REMBRANDT trial; www.trialregister.nl; NTR1849) on the effectiveness of six commonly used dressings, and had a complete POSAS score, i.e. without any missing data. This trial, involving 14 Dutch university and general hospitals, included adult patients who had a single donor site wound (DSW) with a surface area of at least 10 cm$^2$ after split-skin grafting for any indication. All patients gave written informed consent. The study was approved by the medical ethics review boards of the contributing hospitals. Inclusion criteria and study protocol have been described in detail previously.$^{16}$

Observers

Twelve weeks after complete wound healing a group of specialized wound care nurses, surgical nurses, and researchers judged the DSS in vivo using the observers’ part of the POSAS. We defined complete wound healing as re-epithelialization of the total wound surface, i.e. without any remaining scabs.

The POSAS contains seven questions on vascularity, pigmentation, pliability, thickness, relief, surface area, and overall opinion. All items were scored on a 10-point scale, ranging from 1 (best possible outcome) to 10 (worst possible outcome). The caregivers had some, but not extensive, experience in scar assessment, because the POSAS can be used reliably even by inexperienced observers.$^{14}$ Nevertheless, all caregivers were instructed on the use of the POSAS by an expert. Patients and observers scored the POSAS during the same outpatient visit. Patients were asked to rate their scar using the Patient and Observer Scar Assessment Scale, i.e. the patients’ part of the POSAS, containing seven questions about pain, itching, colour, pliability, thickness, relief, and overall opinion. Subsequently, the caregivers also assessed the scar. Caregivers and patients were unaware of each other’s judgment.

Data analysis

We collected basic demographic data of the patients, comprising age, sex, location of the DSS, and mean time to complete wound healing.

Inter-observer agreement

Inter-observer reliability (IOR) regarding the POSAS scores between caregivers and patients was expressed as intra-class correlation coefficient (ICC), including their 95%
Do patients and caregivers agree?

Confidence intervals (CI), using a one-way ANOVA model for single measure agreement. This IOR is the measure we used to assess the agreement between patients and caregivers. The ICC takes values from zero (no agreement) to one (perfect agreement).\(^\text{17}\) We considered an ICC above 0.8 as ‘very good’, between 0.8 and 0.6 as ‘good’, between 0.6 and 0.4 ‘moderate’ and below 0.4 ‘poor’.\(^\text{7}\) The ICC was calculated for all POSAS-items the caregivers and patients had in common. Furthermore, we used the 95\% limits of agreement approach (a.k.a. Bland & Altman plots) to assess the score agreement between the patients’ and observers’ judgment as expressed by the POSAS-items.\(^\text{18}\)

**Prediction of cosmetic satisfaction**

Next to the IOR, we determined which item(s) of the POSAS best predict the overall opinion of patients and caregivers regarding scar cosmetics. We used the same analytic strategy for both patients and caregivers. First, we calculated the Spearman rank correlation for every POSAS item because of non-normal score distributions, with “overall opinion” as the dependent variable.

Subsequently, we included the item with the highest Spearman rank correlation using a forward multivariable regression model. The significance criterion for inclusion of an item in a multivariable regression model was set at a p-value below 0.10. Next, other POSAS-items were entered one by one in the order of their strength of the univariable association with the overall opinion score. A new item was considered relevant to the model if its addition resulted in an absolute increase in R\(^2\) of more than 0.05. Data analysis was carried out using SPSS software (PASW statistics, version 18.0, IBM, Armonk, NY, USA). Due to the non-normal distribution, we conducted a log-transformation of the dependent variable.

**Results**

**Patient and observer characteristics**

We studied 106 patients, including 75 men and 31 women, with a mean age of 59.6 years (SD 16.6, range 18 to 90). Mean time until complete wound healing was 25.3 days (SD 12.4, median 22, range 9 to 65). Most of the DSSs were located on the thigh (n = 102; 96\%), and rarely on the buttock (n = 2; 2\%) or upper arm (n = 2; 2\%). Eleven caregivers judged the DSS, including five specialized wound care nurses, two surgical nurses, and four researchers with a medical or nursing background. They were employed in five different medical centres.
Inter-observer reliability and score agreement

For each common item the IORs between patients and caregivers are shown in Table 1. Agreement regarding their overall judgment of the DSS was ‘moderate’ at best (ICC 0.44, 95% CI 0.27 to 0.58). Agreement regarding the other POSAS-items was ‘poor’, although their 95% CIs were wide. The limits of agreement approach showed that 95% of the overall opinion scores of patients differed up to three points from the caregivers’ scores without a systematic difference (Figure 1).

Table 1. Inter-observer reliability between patients and caregivers

<table>
<thead>
<tr>
<th>Item</th>
<th>ICC</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness</td>
<td>0.31</td>
<td>0.13 – 0.47</td>
</tr>
<tr>
<td>Relief</td>
<td>0.35</td>
<td>0.17 – 0.51</td>
</tr>
<tr>
<td>Pliability</td>
<td>0.38</td>
<td>0.19 – 0.52</td>
</tr>
<tr>
<td>Overall opinion</td>
<td>0.44</td>
<td>0.27 – 0.58</td>
</tr>
</tbody>
</table>

The intra-class correlation coefficient (ICC) was calculated using a one-way ANOVA model for single measure agreement.

Figure 1. Bland & Altman plot of POSAS-scores between patients and caregivers. Each circle represents a donor site scar judged by patient and caregiver; many circles overlap. Difference against mean plot for measurements of overall opinion by patients and observers using the POSAS (mean difference -0.02, SD 1.65)

Items predicting overall judgment

Correlation

For both patients and caregivers, each POSAS item score was significantly associated with their overall opinion (P-value < 0.10). Correlation coefficients ranged from 0.17 to 0.33 in patients, and from 0.22 to 0.50 in caregivers (see Table 2).
Do patients and caregivers agree?

Multivariable analyses

For patients, relief and itching showed the highest association with their overall opinion in the multivariable model (Table 3). Although relief was not significant anymore after adding itching, we forced relief into the model, together with itching, because of the highest association in the univariable analysis. Adding itching to the model explained another 5.1% of the variance in overall opinion score, leading to an $R^2$ of 17.4%. Subsequently, we added and removed each POSAS item to the model with relief and itching, but the $R^2$ did not increase with more than 5%. Together with relief in the multivariable model, itching was statistically the most significant predictor. However, relief discriminated best ($b = 0.13$, 95% CI 0.01 to 0.26, $P$-value = 0.066) (see Table 4). This means that a one-point higher score for relief resulted in a 14% higher overall score of the DSS.

For the caregivers, pliability and pigmentation of the DSS showed the highest association with their overall opinion in the multivariable model and were statistically significant predictors of their overall judgment (Tables 3 and 4). Pliability was statistically the most

Table 2. Associations between POSAS-items and overall opinion of the patients and caregivers. Items with the highest association are stated first.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Caregivers</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSAS-items</td>
<td>Spearman’s correlation coefficient</td>
</tr>
<tr>
<td>Relief</td>
<td>0.33</td>
</tr>
<tr>
<td>Itching</td>
<td>0.30</td>
</tr>
<tr>
<td>Pliability</td>
<td>0.27</td>
</tr>
<tr>
<td>Color</td>
<td>0.26</td>
</tr>
<tr>
<td>Pain</td>
<td>0.23</td>
</tr>
<tr>
<td>Thickness</td>
<td>0.17</td>
</tr>
</tbody>
</table>

POSAS; Patient and Observer Scar Assessment Scale

Table 3. Overview changes in $R^2$ adding POSAS-items

<table>
<thead>
<tr>
<th>Patients</th>
<th>Caregivers</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSAS-item(s)</td>
<td>$R^2*$</td>
</tr>
<tr>
<td>Relief</td>
<td>0.123</td>
</tr>
<tr>
<td>Relief, itching</td>
<td>0.174</td>
</tr>
<tr>
<td>Relief, itching, pliability</td>
<td>0.187</td>
</tr>
<tr>
<td>Relief, itching, color</td>
<td>0.202</td>
</tr>
<tr>
<td>Relief, itching, pain</td>
<td>0.176</td>
</tr>
<tr>
<td>Relief, itching, thickness</td>
<td>0.185</td>
</tr>
</tbody>
</table>

* The correlation coefficient squared ($R^2$) is a measure of the amount of variability in the dependent variable “overall opinion” explained by the other POSAS-items. POSAS; Patient and Observer Scar Assessment Scale.
significant predictor and discriminated best. A one-point higher score for pliability resulted in a 19% higher overall score of the DSS (95% CI 10 to 29%). Adding pigmentation to the model explained another 7.8% of the variance in overall opinion score, resulting in an $R^2$ of 31.8%.

### Discussion

Patients and caregivers use different characteristics when judging the scar of a donor site wound. Itching and relief appear to be the most important characteristic of patients’ overall satisfaction, whereas for caregivers pliability and pigmentation have more impact.

The limited agreement we observed between caregivers and patients is consistent with previous studies in other wound types. O’Toole et al. found that surgeons’ perceptions of cosmetic outcome differed from those of patients with lower extremity traumas.\(^\text{19}\) Kaija et al. found a moderate agreement in cosmetic outcome after conservative treatment of breast cancer.\(^\text{20}\) In our study we found a poor agreement for almost all items of the POSAS (excluding opinion on overall judgment) between caregivers and patients. However, agreement between caregivers in burn- and linear scars has shown to be good.\(^\text{3,14,15}\) So, although the POSAS seems to be a reliable tool in the communication among patients and caregivers they appreciate the scars differently.

Caregivers should realize that the patients’ own view of their scar affects quality of life.\(^\text{21}\) The serious impact of itching on patient satisfaction, as found here, is in accordance with previous studies regarding burn- and linear scars.\(^\text{3,14,22}\) Thus, the proper action of caregivers dealing with scar minimization should be to focus on patient-relevant issues, such as itching and a smooth scar surface. They should encourage patients to value pros and cons of treatment options, so that patients can balance both when deciding with the caregiver for the most suitable treatment option.\(^\text{23}\) These treatments should match the

### Table 4. POSAS-items included in the final model

<table>
<thead>
<tr>
<th>POSAS-item</th>
<th>Unstandardized Coefficient $b$</th>
<th>Standard Error</th>
<th>95% Confidence Interval for $b$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relief</td>
<td>0.13</td>
<td>0.07</td>
<td>-0.01 - 0.26</td>
<td>0.066</td>
</tr>
<tr>
<td>Itching</td>
<td>0.11</td>
<td>0.04</td>
<td>0.02 - 0.20</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Caregivers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pliability</td>
<td>0.17</td>
<td>0.04</td>
<td>0.09 - 0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>0.08</td>
<td>0.02</td>
<td>0.03 - 0.12</td>
<td>0.001</td>
</tr>
</tbody>
</table>

POSAS; Patient and Observer Scar Assessment Scale.
needs and preferences of the patient (e.g. less relief and itching). For donor site wounds, the results of our recently completed trial will help choose the dressing material that best suits this purpose. These considerations are also true for research on scar prevention, where the outcomes patients value the most are often disregarded.

Some limitations of this study should be mentioned. First, we assessed the DSSs after twelve weeks. This is a rather short period, but does allow analysis of the agreement between the patients’ and caregivers’ judgments, which is not likely to improve in the long term. Nevertheless, patient satisfaction may vary in time, especially when the acceptor site is completely healed, and scar characteristics may change even after complete re-epithelialization. After complete maturation of the scar, patients’ overall satisfaction may be more influenced by other items in the POSAS, for example colour instead of itching. Therefore, the predictive value of POSAS-items should be assessed and compared on different time-points. Second, different caregivers judged the wounds, which could influence the results. Yet, this mimics the real life situation in which several caregivers may be involved in the care for such patients. Up to now the agreement among various caregivers regarding their judgment of DSSs remains unclear. Third, although the judgments of patients and caregivers were compared, there was no reference standard with regard to the “truth” about the scar characteristics. This is of minor importance in our study as the patients’ perception seems the ultimate outcome caregivers should deal with, when pursuing the ideal of patient-centred care. Finally, the precision of the agreement we found was limited, as illustrated by the wide confidence intervals. This may imply an insufficient number of patients with DSSs investigated. However, this imprecision does not affect the conclusions of our study, as the upper limit of the ICCs indicated a moderate agreement at best. More patients would likely have narrowed down the confidence intervals to “poor” levels.

We conclude that patients and caregivers adhere to different characteristics of donor site scars. Scar perception is dependent upon many variables, which have different predictive values, depending on the perspective of the assessor. Given this discrepancy, patient preferences should be considered in decision-making on wound treatment and scar prevention options.
References


Do patients’ and caregivers’ perceptions of donor site scar quality change over time?
A follow-up study

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Submitted
Chapter 9

Abstract

Background
The Patient and Observer Scar Assessment Scale (POSAS) involves patients and caregivers to judge scars. Clinical changes in scar perception during scar maturation is poorly investigated, especially in donor site scars (DSS). We investigated patients’ and caregivers’ satisfaction regarding the quality of the DSS and explored possible changes in time.

Methods
Patients after split-skin grafting (n=64) and their caregivers (n=9) evaluated the scars twice using the POSAS, while unaware of each other’s judgment. The first assessment was done three months after complete healing, the second at least six months later.

Results
At the first and second assessment most POSAS-items received low scores, meaning high satisfaction. Nevertheless, the patients’ second judgments of the POSAS-items ‘colour’ (effect size 0.28; P-value=0.001; Wilcoxon test) and ‘total patient scale score’ (effect size 0.19; P-value=0.032) were significantly lower than the first ones. For caregivers, all second judgments of the POSAS-items, with the exception of thickness and pliability, were significantly lower than the first ones. Medium effect sizes were seen for total observer scar scale (0.46), vascularity (0.42), overall satisfaction (0.34) and pigmentation (0.30).

Conclusion
Patients’ and caregivers’ satisfaction regarding scar quality of donor sites is high and improves slightly throughout the scar maturation period.
Introduction

Wound care regimens usually pay little attention to the cosmetic outcome of wound healing, whereas for patients scarring is often their greatest concern. If these scars are located in visible areas, they may have a psychological impact and could affect their quality of life. Scars may cause persistent discomfort; both cosmetically and physically (e.g. colour or itching). A survey in the United States showed that 91% of patients would value even small improvements in scarring. Therefore, the patients’ perception of the quality of their scars has to be taken into account when informing the patient to avoid unrealistic expectations about treatment outcomes.

Caregivers tend to neglect cosmetic scar quality when informing their patients, possibly because the long-term effect of interventions to improve scars is not supported by a large amount of sound evidence. In addition, scar quality is often assessed before the scar has fully matured, while scar maturation is known to take at least 12 months. Another problem is that patients and caregivers value the scar quality differently during its maturation.

To determine the clinical changes of scars in time, a reproducible and valid rating scale is essential. Although none of the scar assessment scales available really stands out or is generally accepted, one of them has been validated, i.e. the Patient and Observer Scar Assessment Scale (POSAS). This scale is unique in that it takes the opinion of the patient into account. The POSAS consists of two scales: the Patient Scar Assessment Scale and the Observer Scar Assessment Scale. Furthermore, it includes all recommended scar measurements items, namely colour, thickness, relief, pliability, surface area.

Previous research showed better scar quality scores after a longer follow-up period using the POSAS. Overall, patients were more satisfied about burn and linear scars after cleft lip surgery if scar assessment was done after a longer time interval. In burn scars, caregivers were more satisfied with the outcome compared to patients. The opposite was found in scars after cleft lip surgery whereas patients were more satisfied. For donor site scars (DSSs) it remains unclear if the perceptions of the scar assessed by caregivers and patients show better outcomes in the long term. These scars are different from others, whilst these linear-shaped scars are acutely created to cover other defects. As a result, patients have to accept this second scar, which could lead to more negative emotions in association with this scar.

Therefore, the aim of our study was to investigate the patients’ and caregivers’ perceptions as to the quality of DSSs and to explore the possible changes in time. We tested the
following hypothesis: patients and caregivers are significantly less satisfied about the quality of the DSS after three months than later in time.

**Methods**

**Patients**

Adult patients with DSSs who had participated in multicentre randomized clinical trial regarding donor site treatment (REMBRANDT trial; www.trialregister.nl; NTR1849) were approached. We selected patients who lived within a reasonable travel distance (< 1 hour) of the Academic Medical Center in the Netherlands. The prerequisites to contribute to this study were the presence of a DSS that had completely healed for at least six months, and a completed baseline POSAS assessment three months after complete healing.

**POSAS**

To rate the quality of their DSS, patients used the Patient Scar Assessment Scale, i.e. the patients’ part of the POSAS, which contains the following six items: pain, itching, colour, pliability, thickness, and relief. The caregivers’ part of the POSAS (i.e. the OSAS) contains the following six items: vascularity, pigmentation, pliability, thickness, relief, and surface area. All items were scored on a 10-point scale, ranging from one (best possible outcome) to ten (worst possible outcome), and results in a ‘total score’, which can add up to a maximum of 60 points.

In addition, patients as well as caregivers assessed their overall satisfaction with the cosmetic appearance of the scar, also on a scale of one to ten, corresponding with the worst imaginable scar.

**Measurements**

Both groups evaluated the scars twice, using the POSAS, at outpatient visits. The first scar assessment was done three months after complete healing of the donor site, the second at least six months after complete closure. We chose the six-month threshold, because developments in scar quality should be visible approximately six to seven months after the skin harvest. Complete wound healing was defined as re-epithelialization of the total wound surface, i.e., without any remaining scabs.

The first scar assessment was done by six caregivers and the second by three caregivers. These caregivers were specialized wound care nurses, surgical nurses, and researchers.
with a clinical background. Caregivers and patients were unaware of each other’s judgment in both assessments.

**Ethical considerations**

The local medical ethics committee waived the need for approval of this study. Willingness to participate was implied when the patients gave written consent for their participating in the REMBRANDT trial.

**Data-analysis**

Patients’ baseline data comprised age, sex, indication for SSG, location of the donor site, time elapsed since the skin harvest, and skin type by using the Fitzpatrick skin classification.\(^1\)

We used the Wilcoxon Signed Rank Test to compare the changes in the POSAS scores between the two assessments. Additionally, we calculated the effect size of a difference found by dividing the Z-value of the Wilcoxon test by the square root of number of observations. We considered an effect size above 0.5 as a ‘large effect’, between 0.3 and 0.5 as a ‘medium effect’, between 0.1 and 0.3 a ‘small effect’, and anything below 0.1 ‘trivial’.\(^1\) Generally, this means that the larger the effect size, the greater the change in scar quality.

Given the various time intervals between both time points, we could further analyse the relationship between the patients’ and caregivers’ overall satisfaction and the age of the scar. The scores of overall satisfaction, measured at the second time-point were plotted to determine its association. If linear, we planned to perform a general linear model.

**Results**

We studied 64 patients, who filled out the POSAS at both time points. Most of them were men (67%), with a mean age of 60.1 years (SD 15.8, range 23 to 90). The first scar assessment for all patients was three months after complete wound healing. The second assessment of the scar was carried out after at least six months, with a mean of 20.3 months (SD 5.6, range 6 to 32) after complete wound healing. The majority of indications for split-skin grafting were acute or traumatic wounds (n = 44; 68.6%). The DSSs were mostly located on the thigh (n = 62; 96.6%) (Table 1).

Caregivers classified the majority of the patients (50%) as having skin type II according to Fitzpatrick (white skin; blond or red hear; blue, green or hazel eyes) (Table 1).
Patients' perception of DSS over time

Table 2 shows the patients' perceptions of the DSS quality at both time points. Two examples of scar appearance are showed in Figures 1 and 2. At the first time point most of the POSAS-items received a low score (range 1 to 6), suggesting that patients were already satisfied with their scar at an early stage (see Table 2). Nevertheless, at the second time point, a further significant reduction was found for the POSAS-items 'colour' (P-value = 0.001) and 'total patient scale score' (P-value = 0.032). This indicates patients had become more satisfied with the quality of the scar for these two items later in time. These changes represented a small effect size for colour (0.28) and total patient scale score (0.19). The other items showed no significant differences in patients' perception between both time points.

Caregivers' perception of DSS over time

Table 3 shows the caregivers' perceptions of the DSS at both time points. Again, at the first time point most of the OSAS items received a low score (range 1 to 4). At the second time point, all items were significantly lower, with the exception of thickness and pliability. Effect sizes were medium for total observer scar scale (0.46), vascularity (0.42),
Table 2. Patients’ perceptions of donor site scar

<table>
<thead>
<tr>
<th></th>
<th>Pain</th>
<th>Itching</th>
<th>Color</th>
<th>Pliability</th>
<th>Thickness</th>
<th>Relief</th>
<th>Overall opinion</th>
<th>Total POSAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Median (IQR)</td>
<td>64</td>
<td>64</td>
<td>63</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Time point 1</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>4 (2-6)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>3 (1-4)</td>
<td>13 (10-16)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>2 (1-5)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>2 (1-4)</td>
<td>9 (8-16)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.131</td>
<td>0.175</td>
<td>0.001*</td>
<td>0.469</td>
<td>0.347</td>
<td>0.843</td>
<td>0.441</td>
<td>0.032*</td>
</tr>
<tr>
<td>Z-score</td>
<td>-1.511</td>
<td>-1.356</td>
<td>-3.179</td>
<td>-0.723</td>
<td>-0.941</td>
<td>-0.198</td>
<td>-0.771</td>
<td>-2.146</td>
</tr>
<tr>
<td>Effect size</td>
<td>0.13</td>
<td>0.12</td>
<td>0.28</td>
<td>0.06</td>
<td>0.08</td>
<td>0.02</td>
<td>0.06</td>
<td>0.19</td>
</tr>
</tbody>
</table>

An effect size above 0.5 was considered as a ‘large effect,’ between 0.3 and 0.5 as a ‘medium effect,’ between 0.1 and 0.3 a ‘small effect,’ and anything below 0.1 ‘trivial.’ * IQR: interquartile range; POSAS: Patient and Observer Scar Assessment Scale.

Figure 1. Difference in scar appearance over time (3 and 13 months after split-skin grafting)

For this patient the total POSAS scores were 42 (out of 60) at time point 1 and 32 at time point 2.
### Table 3. Caregivers’ perception of donor site scar

<table>
<thead>
<tr>
<th></th>
<th>Vascularity</th>
<th>Pigmentation</th>
<th>Thickness</th>
<th>Relief</th>
<th>Pliability</th>
<th>Surface</th>
<th>Overall opinion</th>
<th>Total POSAS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregivers</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Median (IQR) Time point 1</td>
<td>2 (2-3)</td>
<td>3 (2-4)</td>
<td>1 (1-1)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>1 (1-1)</td>
<td>2.5 (2-4)</td>
<td>13 (10-16.75)</td>
</tr>
<tr>
<td>Median (IQR) Time point 2</td>
<td>1 (1-2)</td>
<td>2 (2-3)</td>
<td>1 (1-1)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>1 (1-1)</td>
<td>2 (1-3)</td>
<td>10 (9-13)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.000*</td>
<td>0.001*</td>
<td>0.106</td>
<td>0.011*</td>
<td>0.636</td>
<td>0.020*</td>
<td>0.000*</td>
<td>0.000*</td>
</tr>
<tr>
<td>Z-score</td>
<td>-4.741</td>
<td>-3.480</td>
<td>-1.616</td>
<td>-2.554</td>
<td>-0.473</td>
<td>-2.333</td>
<td>-3.851</td>
<td>-5.169</td>
</tr>
<tr>
<td>Effect size</td>
<td>0.42</td>
<td>0.30</td>
<td>0.14</td>
<td>0.22</td>
<td>0.04</td>
<td>0.21</td>
<td>0.34</td>
<td>0.46</td>
</tr>
</tbody>
</table>

An effect size above 0.5 was considered as a 'large effect', between 0.3 and 0.5 as a 'medium effect', between 0.1 and 0.3 a 'small effect', and anything below 0.1 'trivial'.

* IQR: interquartile range; POSAS: Patient and Observer Scar Assessment Scale.

**Figure 2.** Difference in scar appearance over time (3 and 11 months after split-skin grafting)

For this patient the total POSAS scores were 16 (out of 60) at time point 1 and 18 at time point 2.
overall satisfaction (0.34) and pigmentation (0.3). A small effect size was found for relief (0.22) and scar surface (0.21).

When comparing caregivers’ and patients’ judgments of scar quality, they agreed at both time points as to their overall POSAS scores. Caregivers clearly consider the reduction in vascularity as symptom of scar maturation. This is commensurate with the patients’ observance of an improvement in colour.

**Relationship between patients’ and caregivers’ overall satisfaction and time**

Figures 3 and 4 show the scatter plots of the relationship between patients’ and caregivers’ overall satisfaction and time. No apparent association was found between (P)OSAS-scores and time.

Figure 3. Patients’ overall satisfaction about their scar

Figure 4. Caregivers’ overall satisfaction about the scar
Chapter 9

Discussion

Patients’ and caregivers’ perceptions of the scar quality of donor sites after split-skin grafting change slightly during scar maturation. Apparently, scar condition and satisfaction three months after healing of the donor site wound is likely to improve slightly in the months thereafter. In this study patients and caregivers rated scar quality as high, already three months after healing of the wound, while the magnitude of the observed improvement in satisfaction over time was limited.

The small changes we observed in perception of scar quality and the non-linear relationship with time are consistent with previous studies in other scar types. Van der Wal et al. showed that burn scar quality tends to improve in due course. This improvement starts approximately six months postburn. Furthermore, Bond et al. showed that incisional scars fade after approximately seven months, but still numerous scars retain a reddish appearance after twelve months.

Although patients in our study seemed to be quite satisfied with their scar, it is hard to predict psychological distress based on the severity of disfigurement. For example, Brown et al. found that patients with non-visible scars experienced larger distress than patients with visible scars. Furthermore, Linos et al. concluded that patients with a minimal approach (i.e. smaller incision) were not more satisfied compared to patients receiving the conventional approach in thyroid and parathyroid surgery. This seems to be contradicting the results of the study by Young et al. They noted that patients are highly concerned about the scarring after routine surgery. Most of the patients included in this survey in the USA also felt that caregivers were less concerned about the appearance of the scar than themselves. These results show that scar perception is dependent upon many variables, which may have different predictive value, and are not always measurable with a standard scar assessment scale. Moreover, the minimal difference in POSAS-scores that patients consider to be relevant is unknown.

Some limitations of this study should be mentioned. First, the effect sizes we measured can be relatively large, but the clinical relevance for patients remains unclear. Therefore, the question arises if scar assessment of donor site wounds is important in clinical research. On the other hand, no change in scar quality can be disappointing for patients and a small change in effect size for some items may be more valuable than large changes in other items (e.g. the change in colour may be considerable, but relatively less important to the patient than a smaller change in pain or pigmentation). Besides, the majority of patients were middle-aged men which may not be fully representative for patients undergoing split skin grafting. Second, the scar judgments were performed.
by different caregivers in the long term. The caregivers had some, but not extensive, experience in scar assessment. This could have masked the differences. On the other hand, it is known that the inter-observer agreement of the POSAS is good, even when applied by inexperienced observers.\textsuperscript{22}

Finally, seasonal influences, such as exposure to sunlight, were not taken into account. Despite the missing evidence whether ultra violet (UV)-light has an influence on hyperpigmentation of superficial wounds, clinicians often advise their patients to protect their wounds or scars from UV-light during the first three months. In our study, the majority of the DSSs were located on the thigh, which is usually covered with clothing. Therefore, the possible effect of UV-light on scar quality seems negligible in these patients.

We conclude that patient and caregiver satisfaction as to scar quality of donor sites wounds is high throughout the scar maturation period and improves slightly over time. Assessment of scar quality using the POSAS three months after wound healing seems feasible to appreciate eventual satisfaction. Any improvement is not linearly related to time, but may take a year or two. This notion should be incorporated in the pre-surgical counselling of patients with regard to anticipated anxiety about scar appearance and time needed for scar quality improvement.
References


part III
Guideline development
Richtlijn ‘Wondzorg’ – Aanbevelingen voor 5 knelpunten

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D.T. Ubbink

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Samenvatting

- De interdisciplinaire evidence-based richtlijn ‘Wondzorg’ behelst de behandeling en organisatie van de wondzorg voor volwassenen en kinderen met acute wonden in de gehele zorgketen.
- In de richtlijn worden 5 uitgangsvragen beantwoord met 38 aanbevelingen over reiniging, pijn, instructies aan de patiënt, wondmaterialen en organisatie van wondzorg.
- De richtlijn adviseert onder meer om primair gesloten wonden niet te reinigen, acute open wonden te reinigen met schoon kraanwater, de WHO-pijnladder te gebruiken voor de keuze van analgetica tegen continue wondpijn, lidocaine of prilocaine te geven voor lokale pijnbestrijding bij manipulaties, primair gesloten wonden niet te bedekken met verbandmateriaal, simpele bedekkers te gebruiken voor open wonden en de patiënt heldere instructies mee te geven.
- De richtlijn geeft ook adviezen over registratie, documentatie en overdracht van gegevens over de wond en stelt voor duidelijke afspraken te maken over verwijzingen en verantwoordelijkheden.

Abstract

Guideline ‘Wound Care’: recommendations for 5 challenging areas

- The interdisciplinary evidence-based guideline ‘Wound Care’ covers the treatment and management of acute wounds in adults and children and by all wound care disciplines.
- This guideline answers 5 basic questions with 38 recommendations covering wound cleansing, pain relief, instructing the patient, various dressings and the organisational aspects of wound care.
- The guideline recommendations include not to cleanse wounds that are primarily closed, to cleanse acute open wounds with clean tap water, to use the WHO pain ladder as the basis for the choice of analgesics for continuous wound pain, to administer lidocaine or prilocaine for localized pain relief during manipulation, not to cover primarily closed wounds with dressings, to use simple dressings for open wounds and to give the patient clear instructions.
- The guideline also advises about wound registration, documentation and hand-over of wound care, and recommends making clear agreements about referrals and responsibilities.
Achtergrond

De behandeling van en organisatie rondom patiënten met acute wonden is een aanzienlijk probleem. Dit geldt voor alle zorgprofessionals in de eerste-, tweede- en derdelijn. In Nederland vinden alleen al op de spoedeisende hulp (SEH) jaarlijks naar schatting 420.000 wondzorg gerelateerde behandelingen plaats wegens een verwonding, verbranding of bevriezing.

Zowel de materiële en personele kosten van wondzorg drukken substantieel op het Nederlandse gezondheidszorgbudget. In 2004 bedroeg dit circa €100 miljoen aan materialen (ten laste van ziektekostenverzekeraars) en €1,5 miljard aan indirecte kosten (ziekenhuisopnames, ziekteverzuim, personele kosten, extramurale kosten). Dit is circa 3% van het totale gezondheidszorgbudget.

Deze samenvatting van de evidence-based richtlijn ‘Wondzorg’ behelst de behandeling van patiënten met wonden met een acute etiologie in de gehele zorgketen. Er bestaan reeds nationale richtlijnen voor diverse complexe wonden (zoals diabetische en veneuze ulcer), maar nog geen nationale richtlijnen voor de behandeling van acute wonden.

De richtlijn is bestemd voor alle intra- en extramuraal werkende zorgprofessionals die met wondzorg te maken hebben (bijvoorbeeld: doktersassistenten, huisartsen, verpleegkundigen en specialisten). Het doel is meer uniformiteit en doelmatigheid in de Nederlandse (organisatie van) wondzorg, teneinde de kwaliteit van zorg te verhogen.

Totstandkoming

Deze richtlijn is interdisciplinair ontwikkeld volgens de AGREE-II-methodiek. Een werkgroep van 17 experts identificeerde de 5 belangrijkste knelpunten die de praktijk ervaart met acute wondzorg, waarbij zij zich baseerden op bestaande beleidscontroverses. Dit zijn: reiniging, pijn, instructies, verbandmaterialen en organisatie. De richtlijn beantwoordt de 5 uitgangsvragen in de vorm van aanbevelingen, die zijn opgesteld aan de hand van wetenschappelijke inzichten, overige overwegingen en meningen van experts. Uiteindelijk zijn 38 aanbevelingen geformuleerd, waarvan hier de relevantste worden beschreven. Voor het beoordelen van de methodologische kwaliteit van de gevonden relevante studies is gebruikgemaakt van de GRADE(‘Grading of recommendations assessment, development and evaluation’)-methode.¹
Reiniging en ontsmetting

In de praktijk wordt wondreiniging als een belangrijke component van de wondzorg beschouwd. Wondreiniging en ontsmetting hebben als doel om ‘ideale’ omstandigheden te creëren voor optimale wondgenezing. Reiniging of ontsmetting kan enerzijds contaminatie en infectie voorkomen, maar anderzijds ook mechanische of chemische weefselschade veroorzaken. De werkgroep raadt reiniging aan bij open wonden met vuil (zoals straat-, bijt- of snijwonden) maar niet bij primair gesloten wonden. Figuur 1 toont

Figuur 1. STROOMDIAGRAM Reiniging, ontsmetting en wondmaterialen voor acute wonden
een stroomdiagram voor de werkwijze bij het reinigen en ontsmetten van wonden en het gebruik van wondmaterialen.

Wanneer een wond gereinigd moet worden, adviseert de werkgroep dat met lauwwarm kraanwater te doen en geen ontsmettingsmiddelen te gebruiken. Het gebruik van badjes met huishoudelijke reinigingsoplossingen, zoals Biotex en soda, wordt ontraden vanwege de gevonden schadelijke effecten zoals infectie, vertraagde genezing, maceratie van de huid, maar ook vanwege de extra belasting voor de patiënt. Pas na adequate reiniging zijn antiseptica als jodium of honing, waarvoor de meeste evidence over de effectiviteit ervan bestaat, bruikbaar voor lokaal geïnfecteerde wonden.

Pijnbestrijding

Wondpijn is een veelvoorkomend fenomeen bij zowel kinderen als volwassenen. Het doel van pijnbestrijding bij patiënten met acute wonden is het bewerkstelligen van een comfortabele en snelle genezing. Patiënten met wonden ervaren de verbandwissel als het pijnlijkst, gevolgd door het verwijderen van uitgedroogde of vastgekleefde verbanden. Daarnaast is aangetoond dat onderbehandeling van pijn kan leiden tot chronische pijn. Wondpijn dient daarom voorkómen dan wel behandeld te worden vanwege de impact op de kwaliteit van leven en de verstoring van de normale wondgenezing.

In de praktijk is er controverse over wat de juiste pijnreducerende methoden en middelen zijn. Ook is men vaak onbekend met de eigenschappen van wonden en materialen die wondpijn kunnen veroorzaken, en van materialen die dat kunnen voorkomen. Tabel 1 geeft een overzicht van de manier waarop de pijn bij verschillende oorzaken bestreden kan worden.

Wondpijn wordt in deze richtlijn onderverdeeld in acute wondpijn, veroorzaakt door manipulatie zoals exploratie, chirurgisch wondtoilet, reiniging en verwisselen van verbandmateriaal, en continue wondpijn, waarbij de patiënt pijn ervaart zonder dat manipulatie plaatsvindt. Voor beide soorten wondpijn raadt de werkgroep psychosociale, lokale of systemische behandelingen aan. Voor het systemisch bestrijden van continue wondpijn bij volwassenen raden zij aan om, na overleg met de patiënt, eventueel pijnmedicatie voor te schrijven volgens de WHO-pijnladder. Figuur 2 toont een stroomdiagram voor de pijnbestrijding bij acute wonden.

Voorafgaand aan manipulatie en na overleg met de behandelend arts kan bestrijding van acute wondpijn worden overwogen. Lidocaïne en prilocaïne zijn volgens de werkgroep

**Tabel 1. Wond- en materiaaleigenschappen die pijn veroorzaken**

<table>
<thead>
<tr>
<th>Wondeigenschap</th>
<th>Pijnbestrijding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppervlakkige schaafwonden of donor site wonden</td>
<td>Bescherm de wond en nieuw gevormd epitheel tegen trauma (verbandwissels of verkleving aan kleding) met een vaseline product, folie of hydrocolloidverband.</td>
</tr>
<tr>
<td>Droge wonden</td>
<td>Voorkom uitdroging door een vochtig wondmilieu te behouden door gebruik te maken van een geschikt verbandmateriaal of vaseline producten.</td>
</tr>
<tr>
<td>Wonden die reiniging behoeven.</td>
<td>Preventieve maatregelen tegen wondinfectie. Adequate pijnstilling (systemisch of lokaal) ruim vóór het reinigen (minimaal een half uur). Gebruik een zachte, lauwwarme straal. Denk na over de keuze van het reinigingsmiddel en de concentratie van dit product.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Materiaaleigenschap</th>
<th>Pijnbestrijding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleverige wondbedekkers (bijvoorbeeld droge gazen, alginaat of hydrofiber)</td>
<td>Kennis ten aanzien van de wondbedekkers, wisselfrequentie en het beloop de wondgenezing dient aanwezig te zijn bij zorgverlener en patiënt om pijn te voorkomen. Raadpleeg eventueel de gebruiksinstructies van de leverancier.</td>
</tr>
<tr>
<td>Uitgedroogde wondbedekkers</td>
<td>Gazen tijdig verwisselen of wond beschermen met een vet gaas. Neem de tijd voor het losweken van de gazen en voeg eventueel lokaal lidocaïne of prilocaïne toe, 30 minuten voordat het verband wordt verwijderd.</td>
</tr>
</tbody>
</table>

**Instructies aan de patiënt**

Er bestaat aanzienlijke praktijkvariatie in de mate waarin de patiënt wordt geïnstrueerd. Het doel van instructies over de behandeling en leefregels is het bewerkstelligen van een optimale wondgenezing, dat wil zeggen een fysiologische genezingsduur nastreven, voorkomen van infectie en minimaliseren van de littekenvorming. Om dit te realiseren voor en ook door de patiënt, spelen begrippen als therapietrouw, leefregels en ziekte-
in zicht een belangrijke rol. De patiënt dient volgens de werkgroep ten minste over de volgende zaken te worden geïnstrueerd:

- Hoe een ongecompliceerde wondgenezing verloopt.
- Wat mogelijke complicaties en alarmsymptomen zijn.
- Welke leefregels er gelden (over douchen, mobilisatie of blootstelling aan uv-licht).
- Wat de beste wondverzorging is (zoals het wel of niet bedekken van een wond).
- Wat de contactgegevens zijn van de hoofdbehandelaar en coördinerende zorgverlener.

Uniforme wondzorg en leefregels zijn niet uitsluitend bedoeld om infecties te verminderen, maar dragen ook bij aan optimale ketenzorg en patiënttevredenheid. De voorlichting die een patiënt hierover zou moeten krijgen, staat weergegeven in tabel 2.
Tabel 2. Voorlichting aan de patiënt met een acute wond

<table>
<thead>
<tr>
<th>Wondverzorging</th>
<th>Voorlichting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Het onbedekt laten van een primair</td>
<td>Raad een bedekkend verbandmateriaal bij primair gesloten wonden af.</td>
</tr>
<tr>
<td>gesloten wond</td>
<td>Een wondbedekker dient uitsluitend te worden overwogen;</td>
</tr>
<tr>
<td></td>
<td>• om exsudaat of transudaat op te vangen;</td>
</tr>
<tr>
<td></td>
<td>• indien een patiënt hieraan de voorkeur geeft, ook al is deze op</td>
</tr>
<tr>
<td></td>
<td>de hoogte dat bedekken het infectierisico niet vermindert en het</td>
</tr>
<tr>
<td></td>
<td>verwijderen of verwisselen van verbandmateriaal extra pijn kan</td>
</tr>
<tr>
<td></td>
<td>veroorzaken.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leefregels</th>
<th>Voorlichting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nat worden van de wond</td>
<td>Adviseer om kort te douchen binnen 12 uur (in de eerste lijn) en na</td>
</tr>
<tr>
<td></td>
<td>24 uur (in de tweede lijn) toe te staan, als een patiënt met een primair</td>
</tr>
<tr>
<td></td>
<td>gesloten wond(en) dit wenst.</td>
</tr>
<tr>
<td>Mobilisatie</td>
<td>De operateur dient per patiënt een advies ten aanzien van mobilisatie</td>
</tr>
<tr>
<td></td>
<td>op te stellen. In dit advies spelen persoonlijke voorkeur van de patiënt,</td>
</tr>
<tr>
<td></td>
<td>locatie, verwachte genezingstendens en het type ingreep voorafgaand</td>
</tr>
<tr>
<td></td>
<td>aan de wond een rol.</td>
</tr>
<tr>
<td>Blootstelling aan UV(A)-licht</td>
<td>Oppervlakkige acute wonden (zoals schaafwonden) dienen minimaal drie</td>
</tr>
<tr>
<td></td>
<td>maanden beschermd te worden tegen UV(A)-licht.</td>
</tr>
</tbody>
</table>

Wondmaterialen

Er bestaat binnen en tussen disciplines een grote variatie in de keuze voor wondmaterialen. Het doel van een wondbedekker is om een optimaal wondmilieu te creëren om de genezing te faciliteren, waarbij wordt gestreefd naar een optimale vochtigheidsgraad, zuurgraad en temperatuur. Daarnaast biedt een wondbedekker bescherming en kan deze bloed of wondvocht opvangen.

De praktijkvariatie wordt gevoed doordat de effectiviteit van wondmaterialen bij acute wonden onduidelijk is. Daarnaast zijn er andere factoren die de keuze van een wondmateriaal beïnvloeden, zoals de variatie in wondetiologie en comorbiditeit van de patiënt. Ook bestaan er verschillende visies op de ‘beste’ wondzorg, zowel binnen als tussen disciplines. Tot slot is er een overwegende markt met diverse wond- en verbandmaterialen. Deze materialen vereisen kennis en deskundigheid die in de praktijk vaak ontbreken bij de zorgverlener.

Na adequate reiniging en behandeling van acute wonden worden verschillende wondmaterialen door de werkgroep geadviseerd voor wondbedekking, afhankelijk van het type wond (zie figuur 1). Houd hierbij rekening met

- De wensen van de patiënt (zoals het niet geconfronteerd willen worden met de wond, beperken van mogelijk pijnlijke verbandwissels, snelle wondgenezing en het voorkómen van lekkage van wondvocht op beddengoed of het plakken van kleding aan de wond).
- De materiaaleigenschappen (zoals verwisselfrequentie, (verticaal) absorptievermogen, kleefkracht, occlusief karakter, cytotoxiciteit en pijn).
De kosteneffectiviteit (afhankelijk van benodigde materialen, verwisselfrequentie en personeel).

De beschikbaarheid van het materiaal (zoals aanwezigheid in een apotheek of verpakkingswijze).

Ervaring of deskundigheid ten aanzien van het materiaal en gebruiksgemak.

De vergoeding die de zorgverzekeraar geeft.

Welke afspraken er zijn over het doorverwijsbeleid (bijvoorbeeld bij infectie of wanneer genezing niet optreedt binnen 2 weken).

Organisatie van acute wondzorg

Wondzorg heeft een interdisciplinair karakter, waardoor de overdracht tussen verschillende zorgverlenende disciplines in de ketenzorg van essentieel belang is. Op zorgorganisatie niveau zijn verschillende knelpunten bekend, zoals taakherschikking, onduidelijkheid over wie verantwoordelijk is voor de wondbehandeling, onduidelijkheden over ketenzorg, verschillende wijzen van communicatie, overdracht naar de thuiszorg en tegenstrijdige adviezen. Dit heeft een ongunstig effect op de patiënttevredenheid en de continuïteit en kwaliteit van de geleverde zorg. Een adequate overdracht, onder andere gebaseerd op systematische wondregistratie, is daarom cruciaal.

De werkgroep raadt aan om in de hele keten acute wonden te classificeren en te registreren aan de hand van het rood-geel-zwart-model (waarbij rood staat voor granulatie, geel voor exsudatie en zwart voor necrose) inclusief een classificatie van de vochtigheid (‘droog’, ‘vochtig’ of ‘nat’). Om optimale continuïteit in de ketenzorg te waarborgen dienen daarnaast gegevens overgedragen te worden over wondkenmerken, beloop van de wondgenezing, patiëntkenmerken, diagnose- en behandelplan, te bereiken doelen, en taken en verantwoordelijkheden.

De werkgroep adviseert niet alleen over de overdracht tussen verschillende disciplines maar ook over het door- of terugverwijzen binnen de keten. Er dienen duidelijke afspraken te zijn binnen de regionale keten bij welke indicaties een patiënt naar wie wordt doorverwezen of terugverwezen en wie de behandeling heeft uitgevoerd en wie daarvoor verantwoordelijk is.

Binnen een overdracht dient het wondbeleid schriftelijk te worden vastgelegd, bij voorkeur door een gespecialiseerde wondverpleegkundige, waarbij de wensen en voorkeuren van de patiënt worden meegenomen. Dit wondbeleid kan vervolgens door alle bekwame zorgverleners worden uitgevoerd.
Beschouwing

De richtlijn ‘Wondzorg’ geeft 38 concrete aanbevelingen over acute wondzorg en de organisatie daarvan bij kinderen en volwassenen. De mate van bewijskracht van de beschikbare wetenschappelijke resultaten voor de geformuleerde knelpunten bleek gering, zodat vaak de mening van experts nodig was bij de toestandkoming van de aanbevelingen. Voor een aantal handelingen bij acute wonden is wel overtuigende bewijskracht; hierbij worden echter in de praktijk weinig knelpunten ervaren. Er blijft dus behoefte aan het ontwikkelen van nieuwe kennis op basis van goed opgezet en uitgevoerd onderzoek in de wondzorg, juist voor handelingen waarover wel controverse bestaat.

In de richtlijnontwikkeling is getracht rekening te houden met de praktische uitvoerbaarheid van de aanbevelingen. Daarbij is uitdrukkelijk gelet op factoren die de invoering van de richtlijn in de praktijk kunnen bevorderen of belemmeren. De richtlijn, die nu nog in conceptvorm is, zal worden becommentarieerd door de relevante beroepsverenigingen en vervolgens worden geaccordeerd voor implementatie in de ketenzorg. Een praktijktest zal uiteindelijk uitsluitel kunnen geven over de praktische uitvoerbaarheid.

In de toekomst kan een aantal aanbevelingen omgevormd worden tot indicatoren, die vervolgens gebruikt kunnen worden om de adherentie aan de richtlijn te meten. Bij toekomstige herziening van de richtlijn zal deze kunnen worden verbreed naar andere onderwerpen waarover controverse bestaat, zoals de behandeling met natte verbanden of met antibiotica, of de geschiktste behandeling van letsel aan de vingertop. Verdere ontwikkeling, maar in het bijzonder de implementatie van de richtlijn ‘Wondzorg’, zal een belangrijke bijdrage kunnen leveren aan de uniformiteit en doelmatigheid van de zorg voor patiënten met acute wonden. Wij nodigen u allen uit de volledige tekst van de richtlijn te lezen, te bespreken in uw instelling en als basis te gebruiken voor uw lokale protocollen.
Literatuurlijst


Chapter 11

General discussion
General discussion

Providing evidence-based wound and scar care is challenging. Although the body of knowledge in this field is growing, especially for complex wounds, some areas, like acute wound care, are underrepresented. For this reason, in this thesis I addressed three main topics to enhance and disseminate the body of knowledge: the generation of evidence for (acute) wound care (part I); the assessment and appreciation of scar formation (part II); and the development of an evidence-based guideline for acute wounds (part III). This guideline will assist clinicians in making evidence-based decisions in their daily care of patients with acute wounds.

Evidence generation and availability (part I and part III)

Ideally, evidence-based wound care integrates patient preferences, clinical expertise and the best-available evidence in clinical decision making. Nevertheless, regardless of the strength of the evidence generated and despite attempts to facilitate the availability of this evidence, a discrepancy remains between the ideal and actual wound care.

In the course of this research period I found two types of barriers that could explain the poor integration of convincing evidence in actual wound-care practice:

1. Barriers that affect the availability of convincing evidence; and
2. Barriers that affect the acceptance of convincing evidence (including difficulties in implementing evidence-based clinical guidelines).

Barriers that affect the availability of convincing evidence

An example based on actual wound-care practice was presented in the clinical scenario (Chapter 1). This shows that sterile saline is still being used for wound cleansing even though tap water is equally effective in reducing infections in adult patients. This evidence was presented in a meta-analysis of randomised and quasi-randomised clinical trials first published in 2002, but, despite the available evidence, the practice of using sterile saline for wound cleansing persists. Research findings show that insufficient recognition of available evidence could lead to unnecessary treatments, costs and suboptimal, or even harmful, health care. Given the example above, this is also likely to be the case for wound care.

The fact that available evidence is insufficiently used could, in the first instance, be due to the ever-growing amount of evidence. It is a great challenge for busy clinicians to keep up with the current publication output (Chapter 2). Studies have shown that available evidence on wound care does not reach the practitioners involved. Regular scientific conferences for researchers and caregivers address this problem by rapidly
disseminating (early) research findings to clinicians. Even though this does contribute to the dissemination of the research performed, in wound care this is problematic as only a few of the studies presented at wound-care conferences are subsequently published.\textsuperscript{10,11} Without full publication at a later stage, the conference visitors are left with short abstracts that are difficult to critically appraise, while clinicians who did not visit the conference remain uninformed of the wound-care findings. Despite these drawbacks, the availability and communication of new evidence is a prerequisite for its acceptance and incorporation into clinical practice. Keeping up with the available evidence will require a major change in behaviour, namely evidence-based thinking.

To facilitate this cultural change towards evidence-based thinking, the presentation of the available evidence should be alluring to clinicians. Aggregated, pre-appraised evidence (Chapter 3) and evidence-based guidelines (Chapter 10) should save time for busy clinicians as they reduce the amount of reading that is required and provide rapid insight and valuable recommendations for clinical wound-care practice. Regular journal-club meetings, better access to medical databases, and continuous training on evidence-based wound care are all attempts to present the available evidence in a manner that will be attractive to busy clinicians.

**Barriers that affect the acceptance of convincing evidence**

When clinicians actually read and appraise the available evidence, accepting the recommendations or conclusions becomes the next challenge. In wound care, in particular, expert opinion is often decisive when treating wounds, and it is considered to be a barrier to accepting the latest evidence. This mentality is nurtured by the fact that successful wound care depends not only on the treatment regime of the wound itself but also on factors such as a collaboration between disciplines to provide holistic wound care, and also on patients’ compliance or responsibility. For instance, when actively treating underlying illnesses, such as diabetes mellitus, a suboptimal dressing choice may go undetected as the wound heals gradually. Meanwhile, the clinician feel reassured that ‘his’ dressing material remains the best treatment for the patient, even though the healing is actually due to the systemic treatment.

The paradigm of Evidence-Based Medicine (EBM) could offer wound-care providers (and dressing manufacturers) a more critical attitude and provide them with strategies and tools to interpret and integrate the latest evidence instead of relying on expert opinion.\textsuperscript{12} To bridge the gap between this long-lasting culture of treating wounds based on expert opinion and evidence-based wound care, I would like to stress that clinical guidelines embrace expert opinion while also integrating the available evidence in order to answer
a clinical question or provide a recommendation that takes practical considerations into account (Chapter 10).

Also, one could argue that surgeons do not sufficiently value the importance of (acute) wound care. After treating the initial illness, attention for the subsequent wound healing may weaken. This was clear from the clinical scenario, where the healing of the donor-site wound received less attention, and only the acceptor site was mentioned in transfer communication to the general practitioner (GP). This corresponds with the minimal attention wound treatment receives in the medical and nursing curriculum. In the various chapters of this thesis I emphasise the importance of optimal wound care, as wounds have a great influence on patients, caregivers and the health-care system. Wounds often need intensive care (e.g. frequent dressing changes or cleansing), may cause wound pain, and the scar that remains after healing may differ substantially from the original appearance. Moreover, the optimal initial treatment of acute wounds prevents the development of complex wounds, which are considered to be an even greater health-care problem with prolonged healing times, increased pain, more challenging treatment strategies and higher costs. Hence, wound healing and evidence-based wound care should receive a prominent place in wound practice, with all clinicians receiving continuing education. A strong collaboration between researchers and clinicians should enable the development of evidence-based guidelines. Clinicians could keep the guidelines clinically relevant by means of critically appraised topics and clinicians or policy makers should implement the guidelines through local protocols.

Difficulties in implementing evidence-based clinical guidelines
Awareness is growing that guideline development alone is not enough to provide evidence-based care or to lead to the actual evidence-based behaviour of clinicians. Implementation of a guideline, particularly of a multidisciplinary one, is very complex and requires tailored implementation strategies. Various factors are known to influence the implementation of clinical guidelines, and the implementation of a guideline for ‘acute wound care’ may present additional challenges (Chapter 10).

First, the type of health-care problem may influence the adherence to a clinical guideline. For instance, better compliance was found in the case of acute rather than chronic health-care problems. Even though acute wounds form a substantial health-care problem, they cannot boast a large body of convincing evidence or strong recommendations in guidelines. This is even more poignant because seemingly uneventful acute wounds may become complex wounds. Future implementation strategies for the guideline on acute wound care should emphasise and motivate clinicians with regard to the relevance of ‘acute wound care’ as a health-care problem. This is hampered by the
difficulty that optimum wound care can range from short to intensive wound treatment, i.e. from an abrasion to a complex, necrotic wound. Regardless of the time spent on acute wound care, it is difficult to predict which wounds will heal and which will become complex acute wounds. Implementation strategies should emphasise that optimal acute wound care can avoid the development of complex wounds and their associated burden on the health-care system.

The second issue relating to this health-care problem is the interdisciplinary character of wound care. In the clinical scenario, the patient deals with seven different disciplines (a GP, an emergency room (ER) nurse, an ER doctor, a general surgeon, a plastic surgeon and/or a trauma surgeon, a nurse on the surgical ward, and a wound-care specialist) at three different locations (the GP’s office, the ER, and the surgical hospital ward). To ensure guideline adherence by all wound-care disciplines, every discipline should be involved in the development and dissemination of the guideline.19

Third, the quality of a guideline may contribute to its clinical use and adherence.15 The use of quality-assessment tools (e.g. AGREE II) is recommended during the development and reporting of a guideline. The AGREE II instrument contains six quality-related domains (scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence) that contribute to the inclusion of quality features in guidelines.19 This quality assessment tool was used during the development of the guideline on acute wounds in anticipation of the implementation process.

Several limitations of our guideline in relation to these domains should be mentioned. The scope of our guideline was restricted by financial and practical limitations. Further updates of this guideline should broaden its scope and include other relevant clinical bottlenecks, such as the treatment of burns, negative-pressure therapy, debridement and antimicrobial therapy. Monitoring or auditing criteria should be developed in order to enhance its applicability. Even though this guideline was developed independently of financial stakeholders, the health-insurance industry plays an influential part in current wound-care practice. To prevent incongruity with the wound-care materials provided by health-insurance providers, a provider took part in our guideline development.

In addition, future developments such as translation into English, pilot testing of the usefulness and adherence to the guideline, and the development of an application for smartphones would further contribute to a broad and successful dissemination.

When evidence is generated and clinicians are willing to accept this evidence, the environment has to be conducive to change.3 The general opinion is that new insights
proven by strong evidence should be implemented as they could be less harmful, more effective, or more in accordance with patient preferences. The introduction of new wound-care materials should be supported by strong evidence, because currently the highly profitable and unrestricted market\(^1\) for new wound-care products seldom relies on trials of their effectiveness. On the other hand, we found that strong evidence could fail to reach clinical practice when manufacturers are reluctant to change the indication criteria for a certain drug or dressing (Chapter 3). In wound-care practice, barriers to the uptake of evidence arise at different levels, for example at the level of the clinicians, the department, the pharmacy or the industry. All these barriers need to be studied in order to change local practice, which is a requirement for effective implementation.\(^{20,21}\) Initiatives such as providing the order numbers of wound-care materials, easy-to-use flowcharts or local protocols, and information or education opportunities for innovative wound-care strategies are desirable in order to facilitate a change in practice.\(^{22}\)

Last, but definitely not least, wound care involves many different stakeholders, i.e. patients, doctors, nurses, manufacturers, and pharmacists. All stakeholders take part in and influence the chain of wound care that is actually delivered. This requires the whole chain to work continuously together and within the same paradigm of optimal wound care. Although the industry, the patients and the clinicians could have conflicts of interests, the patients’ well-being should be the top priority. Therefore, I strongly advocate that the paradigm of EBM be used by all stakeholders in order to ensure high-quality wound care. For example, not only should clinicians choose an effective wound-material, but this material also has to be provided by the industry and be made available in the hospital stores. As shown in this example, different stakeholders in wound-care provision should employ evidence-based thinking in order to practice evidence-based wound care. When a single stakeholder refuses to participate in this evidence-based chain of wound care, this stakeholder hampers the eventual evidence-based wound-care practice.\(^{23}\)

**Patient preferences and decision making (part II)**

The findings of part II include not only the accurate assessment of donor-site scars but also, and more importantly, the patients’ satisfaction when judging their scars. Because of their subjective character, pain and scarring are best assessed by the patients themselves. In our experience, clinicians often neglected patient preferences and goals, for example regarding the location or prevention of their donor-site scar, so that shared decision making rarely occurred.

\(^{1}\) Wound-care products merely require trials to demonstrate safety and performance in order to obtain a CE (Conformité Européene) mark.
Chapter 11

During the course of the investigations carried out for this thesis, I observed two specific reasons why shared decision making should be incorporated into daily wound-care practice. First, the plethora of wound-care materials requires that a proper assessment is made of the patients’ preferences with regard to factors such as the frequency of dressing changes, when to shower the wound, the need for analgesics, or the desire to prevent problematic scar formation. Second, the lifelong nature and impact of scars should be an incentive for clinicians to involve patients in medical decision making whenever possible.

Understanding that the preferences or values of the patient may differ from the clinician’s priorities is a first step. The patient might value the risks, benefits and side effects of the treatment options differently. Patient-advocacy organisations play a valuable role in exploring and promoting patients’ goals and preferences, taking into account the fact that the ‘average’ patient does not exist. To date, no advocacy organisation for patients with (acute) wounds exists. Nevertheless, patients’ preferences and values need to be explicit in order for evidence-based wound care to be practised, and alternative solutions for incorporating patients’ preferences should be pursued. Several international stakeholders, as well as some Dutch university hospitals in particular, have recently committed themselves to this leading principle that calls on patients and clinicians to work together to be co-producers of health. Qualitative research and literature reviews of patient values or experiences are useful for revealing patient preferences.

Even though our findings were limited to donor-site scars, which limits the external validity of the studies, we advocate the incorporation of patient preferences and shared decision making in acute wound care. Given the study results presented in this thesis, patient preferences should, and can, play a particular role in the decision-making process regarding the location of the donor-site wound, the promotion of wound healing, and the prevention of scarring.

Concluding remarks and future perspectives

Acute wound care is a complex problem that requires a multifaceted approach, consisting of high-quality research, optimum evidence-based care, and the timely implementation of better treatment options by all healthcare professionals involved. The latter is consistent with the results and experiences observed during the course of this thesis, but has been previously investigated by others. Changing a long-lasting culture is difficult and takes time. We therefore believe that extending our knowledge of (acute) wound care is vital for achieving optimal wound care.

To make this a reality, strong evidence should be generated and properly disseminated among clinicians. To overcome the long-lasting history of experience-based wound care,
EBM should be introduced into the curricula of all wound-care providers and wound-care stakeholders. Then, in order to maintain a critical attitude towards different wound-care strategies, future wound practice should involve regular journal clubs, optimal online and smartphone support, conferences, and updates of local protocols along evidence-based guidelines. As discussed above, the challenges concerning the implementation of new evidence requires a multifaceted, multidisciplinary and tailored approach. For acute wounds in particular, clinicians should be convinced of the relevance and magnitude of this health-care problem and of the consequences of suboptimal wound care. Not only clinicians, but all stakeholders, should collaborate on improving the quality of wound care, as the full cooperation of all involved is needed to provide optimal wound care. Patients, for that matter, are probably the most vital link. Therefore, future research should include patient preferences.

In conclusion, the author of this thesis appeals for an improvement in the quality of acute wound care, where the caregivers’ responsibility is not limited to presenting the evidence according to EBM. Caregivers should also make sure that all available evidence actually reaches patients and, thus, improves the quality of care. Therefore, apart from generating and presenting evidence, an equal amount of attention should be given to the integration of this evidence into daily clinical practice.
References


Appendices
Summary & Samenvatting
Summary

In this thesis, three aspects of wound care have been explored. The first aspect is the generation of evidence for patients with (acute) wounds (part I). The second is the assessment and patients’ appreciation of scar formation, of donor sites in particular (part II). The final aspect is the integration of available evidence with current clinical views and expertise on acute wound care in order to arrive at an interdisciplinary, evidence-based guideline (part III).

Part I: Acute wound healing

Evidence generation in wound care seems to be more difficult than in other medical areas because wound care has to contend with a variety of aetiologies and a diversity of treatment options with differing financial burdens.

In Chapter 2 we describe a longitudinal trend analysis on research in wound care in comparison with breast cancer over the last five decades. The results of this study showed a 30-fold rise in publications on wound care, but a 70-fold increase in those on breast cancer. As well as falling behind on quantity, high-quality study designs and guidelines were less frequently published in wound-care than in breast-cancer research. Despite the discrepancy in the amount of convincing evidence available for wound care in comparison with other areas, we would like to stress that sound evidence is available and recommend that caregivers take the available evidence into account in their decision making.

In order to support this decision making with evidence-based recommendations, we undertook a meta-review, compiling the best available evidence from systematic reviews regarding local and systemic wound care (Chapter 3). On the basis of 44 Cochrane systematic reviews, 109 evidence-based conclusions could be drawn as to the treatment and prevention of venous ulcers (30), acute wounds (30), pressure ulcers (15), diabetic ulcers (14), arterial ulcers (12) and miscellaneous complex wounds (8). This meta-review offered several recommendations, mostly for complex wounds, that are useful for supporting evidence-based decisions in wound care. Also, some niches in knowledge about wound care, such as the treatment of donor-site wounds and the effectiveness of various wound-care materials, were revealed by performing this meta-review. In future wound-care research, these niches should be expanded with high-level evidence.
Summary

Generating this kind of evidence requires a study design that is best suited to answering the clinical question. Therefore, in Chapter 4 we describe how we initiated a joint venture of international experts in wound care in order to propose a framework for the design and conduct of future RCTs on the effectiveness of wound-care interventions.

Unfortunately, upgrading the quality of study designs does not automatically improve the quality of the reporting of wound-care research. Selective reporting of positive study results or adverse events could lead to a reporting bias, emphasising the need for full and transparent reporting of wound-care research. Therefore, with the same international group of wound experts we proposed a step-by-step reporting standard for future RCTs in wound care in Chapter 5.

We applied this design framework and step-by-step reporting standard to a large, multicentre, six-armed RCT (Chapter 6), comparing six promising dressing materials to cover donor-site wounds in 289 adult patients. The time to complete re-epithelialisation was seven days (30%) shorter for hydrocolloid dressings in comparison with the other five dressing materials, namely, alginate, film, gauze, hydrofibre and silicone dressings. Overall pain scores were low, and they were slightly lower with use of film dressings. The infection rate among patients treated with gauze was twice as high as in those who had other dressings. Given the improved healing time, we recommend hydrocolloid dressings for patients with donor-site wounds and advise against the use of gauze because of an increased risk of infection.

Part II: Scar formation

In the trial described in Chapter 6 we made use of the Patient Observer Scar Assessment Tool (POSAS), which is considered to be a reliable and valid tool for enabling both patients and observers to assess scar quality. This quality may be assessed in vivo or from digital photographs. However, it is questionable whether these two methods influence the results of the scar assessment.

In Chapter 7 we addressed this question by means of an inter-method comparison and validity testing of the in vivo and digital photographic assessment of donor-site scars of 119 patients. The results showed that the reliability and agreement between in vivo and digital-photograph assessment of donor-site scars is limited (reliability was moderate at best; intra-class correlation coefficients of 0.47 and 0.45 were obtained) using the Observer Scar Assessment Scale (OSAS). As a consequence, both methods resulted in significantly different scar judgements of donor-site scars. Our findings suggest that
digital photographs are not a valid substitute for *in vivo* assessment of scar quality. We therefore recommend *in vivo* judgement of donor-site scars using the OSAS.

As well as accurate assessment, evaluating the perception of patients with donor-site scars is essential for managing their expectations and for carrying out shared and well-informed decision making.

In **Chapter 8** we report on an investigation of 106 patients and eleven caregivers on their satisfaction with donor-site scars. We also studied which scar characteristics had the most influence on their judgement. The results of this inter-observer analysis showed that patients and caregivers appreciate different aspects of scar characteristics when using the POSAS. Itching and relief best predicted patients’ overall satisfaction with the scar quality, whereas pigmentation and pliability were most predictive for caregivers. This study emphasises the subjective character of scar-quality assessment. We therefore recommend that caregivers realise that a patient’s own appreciation of a scar affects their quality of life.

A follow-up study was initiated to investigate the clinical changes in scar perception of donor-site wounds during scar maturation, as described in **Chapter 9**. Three months after split skin graft surgery and in the longer term, patients and caregivers rate their scar quality as high. Even though the improvement of scar quality over time is limited, it does improve significantly. We recommend incorporating this notion into the pre-surgical communication with patients with regard to their expectations on eventual scar quality.

**Part III: Guideline development**

In Chapter 2 we revealed the remarkably low number of guidelines for wound care and the absence of a guideline for patients with acute wounds. To support caregivers with evidence-based recommendations tailored to the clinical dilemmas they encounter, we developed a national, interdisciplinary and evidence-based guideline (**Chapter 10**).

This guideline, which addresses clinical dilemmas concerning wound cleansing, wound pain, wound-care instructions, dressing materials and the organisation of wound care, was developed via collaboration between medical professionals from ten different disciplines and one health insurer. Wound caregivers and patients experienced these dilemmas as a bottleneck or a dispute in clinical practice.
Summary

For these clinical bottlenecks we formulated 38 recommendations for clinical practice, summarised in two flowcharts. Broad implementation of this guideline by the various professional societies involved is likely to improve the quality of care for patients with acute wounds and reduce practice variation.

Chapter 11 is a discussion of the entire thesis. Several barriers and future perspectives regarding the acceptance of scientific evidence and patient preferences are considered. Altogether, this thesis stands for generating and presenting strong evidence with an equal amount of attention given to the integration of this evidence in daily clinical practice.
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Dit proefschrift richt zich op drie aspecten van de wondzorg. Het eerste deel omvat de totstandkoming van wetenschappelijk bewijs voor effectieve behandeling en verzorging van patiënten met (acute) wonden (deel I). Het tweede deel betreft de beoordeling en de waardering van patiënten met littekenvorming na een specifieke acute wond, namelijk de wond die achterblijft na een huidtransplantatie; een donorsite wond (deel II). Tot slot wordt het beschikbare wetenschappelijk bewijs ten aanzien van geprivilegieerde klinische dilemma’s in de acute wondzorg gecombineerd met klinische expertise om te komen tot de eerste Nederlandse, wetenschappelijk onderbouwde, interdisciplinaire richtlijn voor patiënten met acute wonden (deel III).

Deel I: Acute wond genezing

Wetenschappelijke bewijsvoering lijkt in de wondzorg moeizamer tot stand te komen dan in andere medische vakgebieden. Mogelijke oorzaken hiervoor kunnen zijn: de grote variatie in wondetiologieën, variatie in patiëntkarakteristieken, hoge kosten en de grote diversiteit aan behandelingsmogelijkheden.

In hoofdstuk 2 wordt een longitudinale trendanalyse beschreven die de verschillen in publicaties over wondzorg en over borstkanker in de afgelopen vijftig jaar heeft vergeleken. De resultaten laten een 30-voudige stijging van publicaties zien voor wondzorg in vergelijking met een 70-voudige stijging voor publicaties over borstkanker. Wondzorgpublicaties hebben naast het achterblijven in hoeveelheid, oftewel kwantiteit, ook te maken met achterblijven in sterkte van wetenschappelijke bewijsvoering, oftewel kwaliteit. Er is slechts een gering aantal studies met hoge methodologische kwaliteit gevonden, zoals gerandomiseerde onderzoeken, systematische literatuuronderzoeken of wetenschappelijk onderbouwde richtlijnen. Ondanks het achterblijven van publicaties in de wondzorg is sterk wetenschappelijk bewijs wel degelijk beschikbaar en zou het ook moeten worden toegepast in de besluitvorming door artsen, verpleegkundigen en patiënten over optimale wondzorg.

Om deze besluitvorming te ondersteunen met het best beschikbare wetenschappelijke bewijs beschrijft hoofdstuk 3 een meta-review over 44 systematische literatuuronderzoeken uit de Cochrane Library. Dit geeft een overzicht van lokale en systemische interventies in de wondzorg, inclusief een gradatie voor de sterkte van het wetenschappelijke bewijs. Op grond hiervan zijn in totaal 109 conclusies geformuleerd ten aanzien van de behandeling en preventie van veneuze ulcer (30), acute wonden (30),
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decubitus wonden (15), diabetische ulcera (14), arteriële ulcera (12) en samengestelde complexe wonden (8). Op basis van deze conclusies wordt een aantal wetenschappelijk onderbouwde aanbevelingen gedaan om de besluitvorming te ondersteunen van artsen en verpleegkundigen voor met name patiënten met gecompliceerde wonden. Tot slot stelt dit hoofdstuk enkele kennislacunes in de wondzorg vast met betrekking tot de effectieve behandeling van donor site wonden na een huidtransplantatie en de effectiviteit van vele wondmaterialen voor (acute) wonden. In de toekomst zouden deze niches moeten worden opgevuld met sterk wetenschappelijk bewijs.

Sterk wetenschappelijk bewijs komt tot stand wanneer een klinische onderzoeks vraag wordt beantwoord in wetenschappelijk onderzoek met een deugdelijke studieopzet. Wanneer de vraag het domein ‘effectiviteit’ betreft, zoals in de hierboven vastgestelde kennislacunes (hoofdstuk 3), heeft een gerandomiseerde studie opzet de voorkeur. Echter in hoofdstuk 2 is vastgesteld dat deze studie opzet in de wondzorg weinig voorkomt, vanwege praktische bezwaren die veel wondenexperts menen te hebben. In hoofdstuk 4 is daarom, in samenwerking met internationale wondzorgexperts, een uniforme standaard opgesteld voor de optimale opzet en uitvoering van toekomstige gerandomiseerd klinisch onderzoek naar effectieve wondzorgbehandelingen.

Het uitsluitend verbeteren van een studie opzet en de uitvoering daarvan leidt helaas niet altijd tot een verbetering van de rapportage. Transparante en gestructureerde rapportage is van belang om volledig geïnformeerde besluitvorming mogelijk te maken. Selectieve rapportage van positieve resultaten of complicaties kunnen leiden tot publicatiebias en onjuiste of onvolledige informatie voor de besluitvorming. In hoofdstuk 5 is wederom een standaard geformuleerd met dezelfde experts als vervolg op hoofdstuk 4, die de schrijver van gerandomiseerd klinisch wondonderzoek stap-voor-stap ondersteunt bij de beschrijving van alle studie resultaten (Hoofdstuk 5).

Gebruik makend van de hierboven beschreven schema’s, beschrijft hoofdstuk 6 een multicenter, 6-armige, gerandomiseerde klinische studie (RCT). Hierin zijn de meest gebruikte en veelbelovende verbandmaterialen voor donorsite wonden na een huidtransplantatie onderzocht bij 289 volwassen patiënten. De tijd tot complete wondgenezing was 7 dagen (oftewel 30%) korter bij het gebruik van een hydrocolloïdverband in vergelijking met de vijf overige materialen, te weten alginaten, folies, gazen, hydrofibers en siliconen. De pijn scores waren over het algemeen laag en enigszins lager in de foliegroep. Patiënten die behandeld werden met gaasverbanden hadden een twee maal hogere kans op een infectie van de donorplaats in vergelijking met de andere behandelgroepen. Op basis van de verkorte tijd tot wondgenezing raden we het gebruik van hydrocolloïden aan en op basis van het verhoogde infectierisico raden we het gebruik van gazen af voor patiënten met donorsite wonden.
Deel II: Littekenvorming

In de hierboven beschreven RCT hebben we gebruik gemaakt van een betrouwbare en valide littekenschaal, de ‘Patient Observer Scar Assessment Tool’ (POSAS), waarmee patiënten en zorgverleners de kwaliteit van het litteken kunnen beoordelen. De littekenkwaliteit kan in vivo of door middel van digitale foto’s worden beoordeeld. Echter, het is onduidelijk of deze twee verschillende methodes de resultaten van de littekenkwaliteit beïnvloeden.

In hoofdstuk 7 beschrijft een onderzoek waarin we kijken of in vivo beoordelingen van zorgverleners overeenkwamen met de beoordelingen van zorgverleners van digitale foto’s bij 119 patiënten met donorsite littekens. Daarnaast is de validiteit van het ‘Observer Scar Assessment Tool’ (OSAS) instrument getest met behulp van de resultaten uit de RCT beschreven in hoofdstuk 6. De resultaten van deze inter-methode overeenstemming studie laten een beperkte overeenkomst zien tussen de in vivo beoordelingen en die van digitale foto’s voor donorsite littekens (de intra-class correlatie coëfficiënt op zijn hoogst 0,47 en 0,45) en een gematigde betrouwbaarheid van deze beide methoden. Derhalve leidden beide methoden tot significant verschillende beoordelingen van de donor sites. Op basis van bovenstaande bevindingen lijkt het OSAS instrument voor digitale foto’s geen geschikt vervangend meetinstrument voor donorsite littekens en raden we vooralsnog de in vivo OSAS beoordelingen aan.

Naast het nauwkeurig meten van de littekenkwaliteit, is kennis van het oordeel van de patiënt, oftewel de tevredenheid, essentieel voor de zorgverlener om op de verwachtingen van de patiënt met een donorsite litteken te anticiperen. Tevens speelt die waarneming van de patiënt een belangrijke rol bij een geïnformeerde en gezamenlijke besluitvorming ten aanzien van de wondbehandeling.

In hoofdstuk 8 zijn de waarnemingen van de kwaliteit van het donorsite litteken bij 106 patiënten door 11 zorgverleners vergeleken. Daarnaast onderzochten we welke littekenkarakteristieken de algemene tevredenheid van patiënten of beoordelaars het meest beïnvloelden. De resultaten van deze inter-beoordelaar overeenstemming studie toonden aan dat patiënten en zorgverleners niet overeenstemden wanneer de POSAS werd gebruikt om de kwaliteit van een donorsite litteken te beoordelen. Jeuk en reliëf voorspelden de “algemene tevredenheid” van patiënten het beste. Voor zorgverleners waren pigmentatie en plooibaarheid van het litteken de sterkst voorspellende onderdelen voor hun “algemene tevredenheid”. Resultaten van deze studie benadrukken daarmee het subjectieve karakter van de ervaren littekenkwaliteit en de verschillen die kunnen bestaan tussen de zorgverleners en patiënten. Omdat een litteken wel degelijk invloed
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heeft op de kwaliteit van leven van de patiënt, dient een zorgverlener zich bewust te zijn van het verschil in littekenwaardering tussen patiënt en zorgverlener en daarmee rekening te houden bij de besluitvorming over de wondbehandeling en littekenpreventie.

**Hoofdstuk 9** beschrijft een follow-up studie waarin we de klinische veranderingen van littekenkwaliteit van donorsite littekens onderzochten gedurende de uitrĳping van het litteken. Al drie maanden na de split skin graft operatie en ook na langere tijd beoordeelden patiënten en zorgverleners de littekenkwaliteit als hoog. Gedurende deze follow-up periode is de littekenkwaliteit nog significant verbeterd, ook al was dit maar een klein verschil. We raden dan ook aan om deze klinische verbetering over tijd mee te nemen in de preoperatieve informatie voorziening aan de patiënt. Daarmee wordt bijgedragen aan het scheppen van reële verwachtingen van de patiënt ten aanzien van het donorsite litteken na een huidtransplantatie.

**Deel III: Richtlijnontwikkeling**

De longitudinale trend analyse in hoofdstuk 2 liet opvallend weinig publicaties over richtlijnen zien in de wondzorg en zelfs geen enkele richtlijn voor de behandeling van patiënten met acute wonden. Om zorgverleners toch te ondersteunen met op maat gemaakte en door wetenschap onderbouwde aanbevelingen voor klinische dilemma's in de acute wondzorg, hebben we een landelijke interdisciplinaire richtlijn ontwikkeld volgens de algemeen geldende Evidence-Based Richtlijn Ontwikkelmethode (**Hoofdstuk 10**).

Met 10 verschillende disciplines en een zorgverzekeraar behandelt deze richtlijn klinische vraagstukken betreffende wondreiniging, pijnbestrijding, instructies aan de patiënt, verbandmaterialen en organisatie van wondzorg. Uit een knelpunten analyse is gebleken dat deze onderwerpen door zorgverleners en patiënten als dilemma's of controverses in de praktijk worden ervaren.

De richtlijn geeft een antwoord op de vijf bovenstaande vragen met 38 aanbevelingen die grotendeels zijn samengevat in twee stroomdiagrammen. De stroomdiagrammen bieden zorgverleners keuze ondersteuning voor de methode van reiniging, verbandmaterialen en zowel systemische als lokale pijnbestrijding. Wanneer deze richtlijn wordt geïmplementeerd en nageleefd door de betrokken disciplines zal dat hoogstwaarschijnlijk de kwaliteit van de acute wondzorg voor patiënten verbeteren en de huidige variatie in deze zorg doen afnemen.
Tot slot bediscussiëren we in hoofdstuk 11 het gehele proefschrift. Waarbij problemen en toekomstige perspectieven ten aanzien van acceptatie van wetenschappelijk bewijs en patiënten voorkeuren worden beschreven. In dit proefschrift pleiten we niet alleen voor de ontwikkeling van sterk wetenschappelijk bewijs maar ook voor de integratie van dit bewijs in de dagelijkse praktijk.
Dankwoord
Dankwoord

*In elke hoge vreugde mengt zich een gevoel van dankbaarheid – Marie von Ebner-Eschenbach*

Nu de afronding van mijn proefschrift dan toch echt dichterbij komt, mag ook ik iedereen bedanken die hieraan heeft bijgedragen. Ik hoop dat ik die dankbaarheid al eerder heb laten blijken maar bij deze dan ook nog op gepaste wijze op papier.

Allereerst de vele patiënten die bereid waren deel te nemen dit wetenschappelijk onderzoek, daarvoor dagelijks dagboeken hebben ingevuld, ons in huis welkom hebben geheten voor follow up controles en bovenal mij (in tijden van computers en papierwerk) verbonden hielden met de kliniek.

Geachte leden van de leescommissie: Prof. dr. T. van Achterberg, Dr. P.M.N.Y.H. Go, Prof. dr. J.B.L. Hoekstra, Prof. dr. D.A. Legemate, Dr. J.R. Mekkes, Prof. dr. J.A. Swinkels en Prof. dr. P.P.M. van Zuijlen. Ontzettend veel dank voor het kritisch doornemen van dit proefschrift, in de zomer, en uw bereidheid om zitting te nemen in deze promotiecommissie.

*Verzamel interessante mensen om mee samen te werken – World of Science course Graduate School*

Mijn promotoren prof. dr. C.M.A.M. van der Horst en prof. dr. J.C. Goslings. Beste Chantal, sinds ons eerste overleg heeft u mij voortdurend geënthousiasmeerd en geïnspireerd voor de wetenschap en organisatie van wondzorg. Daarnaast wist u de het klinische relevantie altijd helder te beschrijven wat voor de publicaties onmisbaar is geweest. Ik ben u zeer dankbaar voor u tijd die u hieraan heeft gewijd.

Beste Carel, u bent intensief betrokken geweest bij de hoofdstukken waar ik zelf erg trots op ben (hoofdstuk 6 en 10). Ik ben u veel dank verschuldigd voor u nauwkeurige en ondanks u overvolle agenda altijd snelle reactie op stukken of vragen van mij.

*It takes two to tango*

Dankwoord

Lieve Hester, van jou heb ik ook heel veel geleerd maar buiten mijn verwachting van wat ik zou leren tijdens een promotietraject. Het interdisciplinaire karakter, je ervaringen in het AMC en je ambitie om kwalitatief goede zorg en onderwijs te leveren kennen geen limiet. Je hebt mij veranderd als dokter en daar ben ik je zeer dankbaar voor.

*I can’t paint the way the want me to paint and they know that too – Rembrandt*

Beste Dirk, Hester en Anne, onzettend veel dank dat jullie mij hebben betrokken bij de REMBRANDT trial. Ik ben altijd enorm trots geweest op deze methodologisch sterke en interdisciplinaire studie. Het was een intensieve en prettige samenwerking waarbij we elke kans aangrepen om dat te vieren met een etentje, chocola, taart of Jip en Janneke champagne gewoon op A3-501.

Lieve Anne, ik weet niet of mate van volgorde waarin je mensen bedankt nog overeenkomt met mate van dankbaarheid, maar ik geloof het niet. Dus ondanks het feit dat ik er in deze zevende alinea aan toe kom, wil ik je bedanken voor je super collegiale en gezellige samenwerking. Wij waren de ‘meisjes van de REMBRANDT trial’, de ‘wond-meisjes’, de ‘meisjes van de roze boekjes’ en ga zo maar door. Ook al ben ik later aangeschoven jij hebt mij toevertrouwd aan je nauwkeurige, systematische en kleurrijke manier van dataverzameling. Het samen uitvoeren van een grote studie is niet alleen praktisch maar ook heel erg gezellig. Zoals je zelf in je proefschrift al schreef hebben we onze onderzoeksperiode op de KPI af kunnen sluiten met een briljant congres (lees: Hilton Hotel in NY, limousines en eten in the Meat Packing Discrict).

Collega’s op de Kwaliteit en Proces Innovatie, ruim drie jaar heb ik als één van de weinige onderzoekers in het AMC kunnen werken op een afdeling met een overvol aan zonlicht. En al die UV straling kwam de sfeer ten goede.
Beste Piet, als baas van de KPI was je op papier niet betrokken bij mijn proefschrift maar dat heb ik nooit zo ervaren. Regelmatig kwam je informeren naar de laatste stand van zaken en was oprecht geïnteresseerd in de voortgang van mijn proefschrift, heel veel dank hiervoor.
Lieve lieve Astrid, Linda, Delphine en Hester, zonder jullie te kort te doen wil ik jullie bedanken voor jullie moederlijke adviezen, tips en vooral het uitwisselen van verhalen. Als groentje hebben jullie me soms geprobeerd te sturen, remmen en me vooral doen beseffen dat ik ook moest genieten!
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Alle collega’s die zijn betrokken bij onze multicenter studie en het schrijven van de landelijke richtlijn voor acute wondzorg.

*Coca cola light break*


Marieke, Josje en Laura heel veel dank voor al het werk dat jullie verzet hebben bij verschillende onderzoeken. Evelien en Sieta heel veel dank voor jullie inzet en hulp bij ‘Geheid Ontslag Beleid’.

*Logica brengt je van A naar B. Verbeelding brengt je overal.*

Lieve paranimfen Lea en Linn. Jullie zijn door mijn hele promotietraject ontzettend betrokken en oprecht geïnteresseerd geweest. Het is dan ook een grote eer en opluchting dat jullie naast me zullen staan tijdens mijn verdediging.

Lea, je bent mijn lievelings-nichtje (zo nou staat dat ook eens geschreven) en onze avonden met kaas en rode wijn blijft een eindeloos recept.

Lieve Linn, ik bewonder je kracht en je verwondering voor de mooie (kleine) dingen in het leven. Ik heb het enorm getroffen met jou als goede vriendin.

Lieve Kiki en Janne, mijn geleerde lieve tantes, heel veel dank voor jullie aanmoediging tijdens dit traject!

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Lieve Gerrie, André, Anne-Roos en Robert, heel veel dank voor jullie interesse en steun.
Dankwoord

Mede mogelijk gemaakt door...

Lieve papa en mama, al wint ‘nature’ het steeds vaker van ‘nurture’ ik zou dat bij deze graag nog één keer tegenspreken. Dankzij jullie eindeloze steun, vertrouwen, enthousiasme, opvoeding en onvoorwaardelijk liefde heb ik de laatste letters kunnen tikken van dit boek. Mama, mijn dank is groot en zal alleen maar groter worden, jou liefde voor je kinderen en kleinkinderen is groter dan eenieder zich kan wensen. Papa, je bent mijn grote voorbeeld (‘nature’ ben ik dus ook erg blij mee).

Woorden schieten tekort

Lieve Lily en Kate, mijn dochters, jullie zijn mijn engeltjes. Elke dag begint en eindigt met een intens gevoel van geluk als ik jullie zie. Mijn liefde voor jullie is onvoorwaardelijk. Lily, wat ben je knap, lief en mooi. Kate jij hebt je eerste drie maanden zo lief geslapen op het zachte geluid van mijn tikkende toetsenbord, jouw bijdrage was onmisbaar voor een succesvolle afronding van mijn promotie.

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Curriculum Vitae
Curriculum Vitae

Chapter 3

PhD Portfolio
# PhD portfolio

Name PhD student: Fleur E. Brölmann  
PhD period: April 2010 – February 2013  
Name PhD supervisors: Prof. dr. C.M.A.M. van der Horst, Prof. dr. J.C. Goslings  
Name PhD co-supervisors: Dr. D.T. Ubbink, Dr. H. Vermeulen

**PhD training**

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<td>Surgery research meeting (1 per week; 42 in total)</td>
<td>2010-2012</td>
<td>0.75</td>
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**Teaching**

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<tr>
<th>Workshops</th>
<th>Year</th>
<th>Workload (ECTS)</th>
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<tbody>
<tr>
<td>Evidence-based Surgery</td>
<td>2011</td>
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<tr>
<td>Wound care</td>
<td>2010</td>
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<tr>
<td><strong>Tutoring, mentoring</strong></td>
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<tr>
<td>Tutoring four students</td>
<td>2010-2013</td>
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</tbody>
</table>

NB. 1 ECTS = 28 hours, based on the European Credit Transfer System
List of publications and press releases
List of publications

National publications

2013

Ubbink DT, Brölmann FE, Vermeulen H. Wondzorg: Wat Weten We Wel? Nederlands Tijdschrift voor Wondgenezing [in press].


2012
Ubbink DT, Brölmann F. Bacteriën en wondzorg. WCS 2012.


2010

International publications

2013


List of publications and press releases


2012


2011

Eskes AM, Bröllmann FE, Gerbens LA, Ubbink DT, Vermeulen H. Which dressing do donor site wounds need?: study protocol for a randomized controlled trial. Trials 2011;12(1):229.
## Press releases

### National evidence-based guideline ‘Wondzorg’

<table>
<thead>
<tr>
<th>Issued, date</th>
<th>Title</th>
<th>Country</th>
<th>Notes</th>
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<tbody>
<tr>
<td>27-6-2013</td>
<td>Geen sodabadje bij acute wonder</td>
<td>The Netherlands</td>
<td>Medisch contact</td>
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<td>2013</td>
<td>Nieuwe richtlijn ontraadt biotexbadje bij acute wond</td>
<td>The Netherlands</td>
<td>Nursing, V&amp;VN, zorgnieuws.</td>
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<td>2013</td>
<td>Evidence-based richtlijn voor de behandeling voor patiënten met acute wonden</td>
<td>The Netherlands</td>
<td>NOVW</td>
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### How To Treat Donor Site Wounds: An Evidence Based Approach. Veith conference 2012

<table>
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<th>Country</th>
<th>Notes</th>
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<tr>
<td>14-11-2012</td>
<td>Hydrocolloid Outdoes Gauze as Wound Dressing</td>
<td>USA</td>
<td>Family Practice News</td>
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</table>

### Evidence-based decisions for local and systemic wound care. *Br J Surg. 2012 Sep;99(9):1172-83*

<table>
<thead>
<tr>
<th>Issued, date</th>
<th>Title</th>
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<th>Notes</th>
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<tr>
<td>28-8-2012</td>
<td>[Onomstotelijk bewijs: hyperbare zuurstoftherapie vermindert risico op grote amputaties]</td>
<td>The Netherlands</td>
<td>Instituut voor hyperbare geneeskunde</td>
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<td>[Onomstotelijk bewijs]</td>
<td>The Netherlands</td>
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<td>24-9-2012</td>
<td>For burn wounds the use of silver sulfadiazine should be discouraged</td>
<td>CHINA</td>
<td>MEBO human body regeneration sciences</td>
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<td>9-6-2012</td>
<td>Association for the Advancement of Wound Care</td>
<td>USA</td>
<td>Multi-disciplinary not-for-profit organisation. US-based with global membership</td>
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<td>9-6-2012</td>
<td>Infection Control Today</td>
<td>USA</td>
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<td>19-6-2012</td>
<td>Nursing Times</td>
<td>UK</td>
<td>Premier UK nursing title</td>
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<tr>
<td>Rolling news</td>
<td>Wound Care Advisor</td>
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<td>Journal website, affiliated with the National Alliance of Woundcare and American Nurse Today</td>
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<td>Symposium on Advanced Wound Care at the North American Center for Continuing Medical Education</td>
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<td>Specialist recruitment agency</td>
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<td>Wound Care Jobs</td>
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<td>Cardiovascular and Metabolic Health Foundation</td>
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<td>Facebook site for annual primary care conference</td>
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<td>11-6-2012</td>
<td>New Cardiovascular Horizons</td>
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<td>19-6-2012</td>
<td>The Nursing Daily</td>
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<td>Anaesthesia UK (FRCA.co.uk)</td>
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<td>9-6-2012</td>
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<td>10-6-2012</td>
<td>Diabetes Daily News</td>
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<td>9-6-2012</td>
<td>e! Science News</td>
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<td>10-6-2012</td>
<td>Endocrinology Daily News</td>
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<td>India Locals</td>
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<td>Rolling</td>
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<td>12-6-2012</td>
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<td>10-6-2012</td>
<td>Medical News Today - website plus various Twitter feeds</td>
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<td>9-6-2012</td>
<td>Malaysia Sun</td>
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<td>9-6-2012</td>
<td>Toronto Telegraph</td>
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<td>247 Professional Health</td>
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<td>9-6-2012</td>
<td>Cochrane-Based Meta-Review Clarifies Treatment Guidelines for Acute and Chronic Wound Care</td>
<td>DGNews – DocGuide</td>
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List of publications and press releases